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THE EFFECT OF TRIETHYLENE THIOPHOSPHORAMIDE IN THE TREATMENT OF LEUKEMIA AND CERTAIN LYMPHOMAS IN INFANTS AND CHILDREN

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NITROGEN mustard, triethylene melamine, and other of the ethylenimines are known to retard the growth of various tumors in experimental animals and in human subjects. Recently, Shay and associates[1] have succeeded in inducing various types of leukemia in rats and thus it has been possible to measure the activity of many ethylenimine derivatives against experimental leukemia in these animals. Among the compounds producing the most satisfactory temporary control of myeloid leukemia in the rat has been N, N′, N″, triethylene thiophosphoramide. From experience in a series of animal experiments it was apparent that this material warranted clinical trial in the treatment of human leukemia. Its usefulness, especially in chronic lymphocytic and chronic myelocytic leukemia in man, has been reported recently.[2]

The chemical relationship of this compound to other ethylenimines is shown by the structural formulas in Fig. 1.

Treatment of a large number of patients with leukemia, lymphomas, and inoperable malignant growths of various types was begun in November, 1952. In the ensuing twelve-month period a large number of adults and twenty-one children were treated with thio-TEPA. The experience with the pediatric patients in this group is the subject of this report. In the early weeks of these observations the drug was given to almost all the children with leukemia and other lymphomas being treated in this clinic. It soon became apparent that the drug was unsuitable for treatment of certain leukemias and thus, subsequently, patients were selected for treatment on the basis of the results of this early experience.

Twenty-one patients under the age of 15 years were treated with triethylene thiophosphoramide (thio-TEPA) in the twelve-month period. There were twelve children with acute leukemia, three with differentiated types of myelocytic leukemia,

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five with lymphosarcoma, and one patient with Hodgkin's disease. The results of these therapeutic trials are summarized in Table I.

The diagnosis of each patient was established by careful clinical evaluation and confirmed by study of the peripheral blood smears and aspiration biopsy of the bone marrow. Surgical biopsies of affected lymph nodes were obtained in the patients with lymphosarcoma and Hodgkin's disease. The patients were re-evaluated prior to starting thio-TEPA, and the bone marrow aspiration biopsy was repeated at that time. Daily peripheral blood studies were made during the course of therapy. The bone marrow was examined at appropriate intervals during the course of treatment.

Thio-TEPA is soluble in isotonic sodium chloride solution. The material was given intramuscularly or intravenously, dissolved in a concentration of 10 mg. per cubic centimeter in isotonic saline. In two patients the material was also given orally in tablet form. Doses were given no more frequently than once a day in 2, 5, or 10 mg. amounts. The amount given at any one time was determined by the clinical and hematological findings immediately preceding the dose. The specific plan of therapy was of necessity individualized for each patient.

RESULTS

Acute Leukemia.—Twelve patients with acute leukemia were treated during the early weeks of our observations. It was impossible for us to distinguish with any degree of confidence whether the very immature cells which had completely replaced the normal bone marrow elements in these patients were of lymphoid or myeloid origin. Ten of the twelve patients had had previous therapy with either folic acid antagonists, roentgen irradiation, or cortisone. In many instances the patients were critically ill at the time therapy with thio-TEPA was begun. Nine of the patients had rather marked splenomegaly, lymphadenopathy, and striking manifestations of hypermetabolism with fever, anorexia, and weight loss. Five of the twelve patients had leukocyte counts that were 13,000 per cubic millimeter or higher when therapy was begun. In the remaining seven patients the leukocyte count was lower than normal. Bone marrow aspiration biopsies showed a striking degree of cellularity in each instance; there was extensive replacement of normal hematopoietic tissue with very immature and undifferentiated leukocyte precursors.

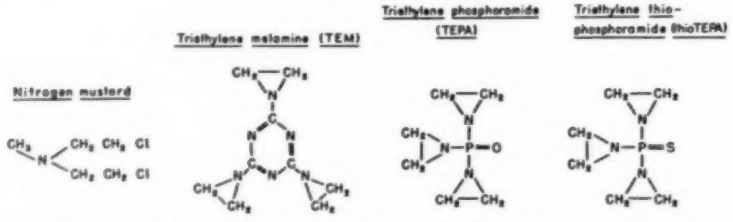

Fig. 1.—The chemical configuration of ethylenimines used therapeutically.

The results of treatment in this group of patients with leukemia were uniformly poor. In only two children did a short period of clinical and hematological improvement follow the administration of the drug. In the other ten patients the course was strikingly similar. Within three to five days after therapy was started with thio-TEPA, definite signs of clinical improvement were noted. Signs of hypermetabolism, i.e., fever, fatigue, anorexia, and the like were strikingly relieved. The lymph nodes, spleen, and liver rapidly diminished in size, with relief of symptoms that might be due to their enlargement. In those patients in whom there was a significant degree of leukocytosis, a precipitous fall in the leukocyte count occurred. The period of clinical improvement lasted only from two to five days, after which time evidences of serious bleeding or overwhelming sepsis appeared. Death would then occur within a few days. It was not possible to alter this disturbing course of events by reducing the initial dose of the drug by using cortisone during the thio-TEPA therapy or by giving large doses of cysteine hydrochloride. On the basis of this experience in twelve patients with acute undifferentiated leukemia of childhood, it would appear that thio-TEPA had been of no value in the treatment of this disease.

The clinical course of a patient with acute leukemia is recorded in Fig. 2.

J. B., a 30-month-old boy, was well until Sept. 4, 1952, at which time he was taken to his family physician because of persistent and excessive bruising. Laboratory studies at that time revealed a rather marked degree of anemia and changes in the leukocytes which were said to be diagnostic of acute leukemia. Between September 5 and 19, he received three doses of cortisone, several blood transfusions, and an eleven-day course of Aminopterin. He continued taking 0.5 mg. of Aminopterin every other day until October 15, after which time severe symptoms of Aminopterin toxicity were noted. Hematuria and melena were present. He was given cortisone, blood transfusions, and antibiotics for a ten-day period and was again improving when he experienced a severe transfusion reaction. Following this episode he responded quite well to additional transfusions, and was discharged from his local hospital on Nov. 6, 1952. One week later he was readmitted to the hospital with a fever of 106° F. and was given several antibiotics and one blood transfusion, and on November 19 was transferred to St. Christopher's Hospital for Children.

At the time of admission the patient appeared pale, apprehensive, and was perspiring profusely. Many subcutaneous hemorrhages were found, especially over the lower extremities. Rather strikingly lymphadenopathy was present in the anterior and posterior cervical regions, in the axillae bilaterally, and in the inguinal areas. The liver edge was palpable 3.5 cm. below the right costal margin and the spleen edge was 12.0 cm. below the left costal border.

The peripheral blood changes and the findings of the bone marrow aspiration confirmed the diagnosis of acute leukemia of an undifferentiated cell type. Treatment with triethylene thiophosphoramide was begun on November 22 and was continued for three days.

The patient showed definite clinical improvement within thirty-six hours after therapy was begun and continued to appear clinically improved for five days. During this time the lymph nodes had strikingly decreased in size and were barely

palpable in most areas. The spleen had become much smaller with the lower border palpable 5 cm. below the costal margin. On November 30 the patient was noted to be icteric, frequent tarry stools were passed, and he died ten days after therapy had begun.

The course of this patient was strikingly similar to that observed in other children in the group with acute leukemia It would appear that the antineoplastic agent had a potent lytic effect against the leukemic cells, readily destroyed the leukemic tissue

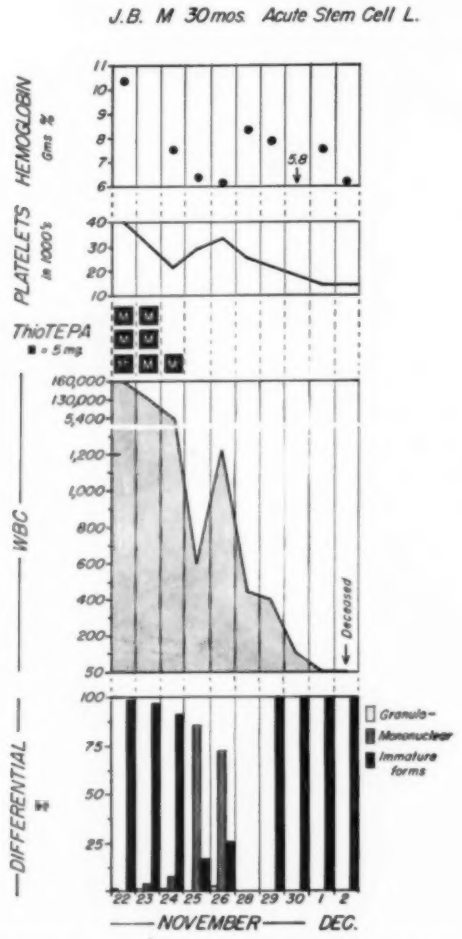

Fig. 2.—The hematological response of acute leukemia to treatment with thio-TEPA.

A bone marrow aspiration biopsy two days prior to death revealed a paucity of cells in the specimen with a complete absence of any normal hematopoietic elements.

in the marrow, in the peripheral lymph nodes, and elsewhere in the body. The inability of functional leukocyte precursors to appear and

assume their leukopoietic function at this time resulted in the death of the patient. There were neither clinical nor laboratory evidences of other toxic manifestations due to the administration of the thio-TEPA. None of the patients showed any signs of return of the bone marrow to normal function after the disappearance of the leukemic overgrowth at this site.

Lymphosarcoma.—Five children with lymphosarcoma were treated with thio-TEPA during the course of these observations. In each instance the patient had enlargement of lymph nodes; there was minimal, if any, discernible involvement of the bone marrow. The mediastinal lymph nodes were enlarged in all of these patients, two of them having severe respiratory distress as the presenting complaint. The patients responded promptly to administration of thio-TEPA with rapid reduction in the size of the involved nodes. When fever was present prior to therapy it promptly disappeared as the tumor masses diminished in size. Respiratory difficulty disappeared as the mediastinal lymphadenopathy was reduced. In three patients the symptomatic relief was of relatively short duration and the patients failed to show improvement on subsequent courses of therapy. Death followed extensive involvement of the bone marrow with bone marrow failure and leukemia.

The course of the disease under thio-TEPA therapy was less acute in the two remaining patients. They were the older members of the group; the onset had been less acute, the response to therapy was less dramatic, and the course more prolonged. There was definite reduction in the tumor masses, bone marrow depression of a clinically significant degree was easily avoided, and temporary clinical improvement resulted from therapy.

The clinical course of a representative patient with lymphosarcoma is recorded below. The hematological changes are recorded in Fig. 3.

M. G., a 5-year-old white male, had a mild upper respiratory infection in September, 1952. Following apparent recovery from this mild disease, he had occasional episodes of cough, and on October 2 was noted to have a moderate degree of swelling on both sides of his neck, anteriorly. The symptoms of cough became more persistent, and some shortness of breath was noted. His family physician found extensive pleural effusion on the left, and repeated thoracenteses were performed. He was admitted for study on Oct. 20, 1952.

At the time of admission to the hospital, there were masses of enlarged cervical lymph nodes visible bilaterally both anteriorly and posteriorly. Large axillary and inguinal lymph nodes were present. The entire left hemithorax was filled with an extensive pleural effusion. The mediastinum was shifted markedly to the right, and on roentgen examination of the chest, the mediastinum measured 10.5 cm. in width. The lower margin of the spleen was palpable 6.0 cm. below the costal margin on the left and the liver edge was 1.0 cm. below the costal margin on the right.

Examination of the bone marrow revealed many immature leukocyte precursors, although there were abundant areas of normal marrow elements.

Triethylene thiophosphoramide was started on Nov. 1, 1952. During the first days of therapy there was little change in the patient's clinical status. The dose of the drug was then

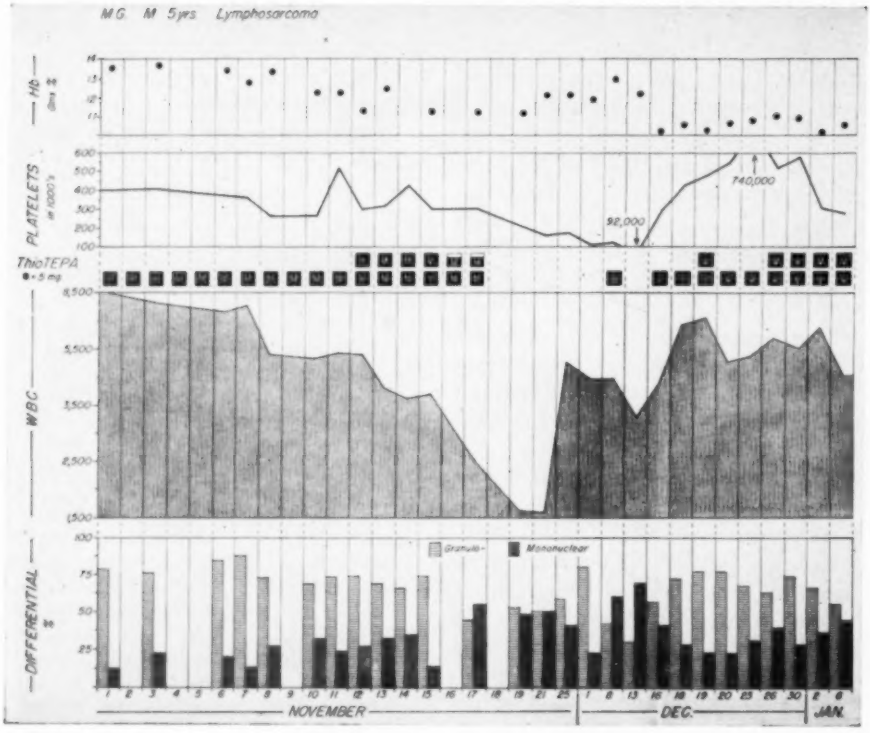

Fig. 3.—The hematological response of patient M. G. with lymphosarcoma to thio-TEPA.

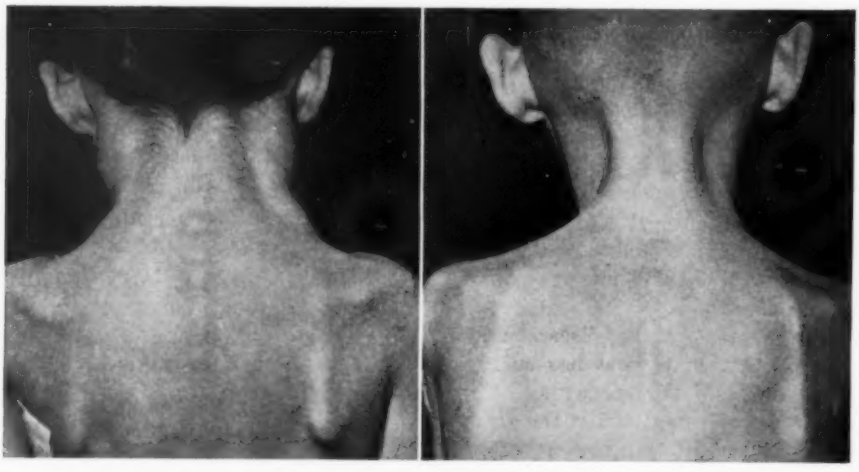

Fig. 4.—Patient M. G. The posterior cervical lymphadenopathy responded dramatically to the initial course of thio-TEPA. The interval between the two photographs was four days.

doubled, and on one occasion it was given intravenously. Within three days after the onset of this more vigorous therapy there followed a complete disappearance of lymphadenopathy and the splenomegaly was considerably reduced (Fig. 4). The patient remained relatively free of symptoms for a few weeks. By Jan. 6, 1953, the mediastinal mass was found to be larger than at the start of therapy. Lymphosarcomatous masses appeared in the retropharyngeal and retroperitoneal areas which did not respond to the administration of large doses of thio-TEPA given intravenously. The patient received roentgen therapy administered locally to these masses with little benefit and died with acute respiratory obstruction on Feb. 7, 1953.

From these limited observations, which are now being extended, it would appear that thio-TEPA is a useful agent for the temporary relief of symptoms of lymphosarcoma. Experience in adult patients has been somewhat more satisfactory than in children. This agent produced results equally as good as have been obtained with other chemotherapeutic agents, and the toxic manifestations of the drug were more easily avoided than with other ethylenimine derivatives. The widespread systemic action resulting from the use of a chemotherapeutic agent has the obvious advantage of generalized antineoplastic effect which is not obtained by the administration of local, symptomatic roentgen-ray therapy.

Myelogenous Leukemia.—Three children with well-differentiated myelogenous leukemia of a subacute or chronic nature were treated with thio-TEPA. One patient who had had the disease for a period of twenty months without prior therapy was treated in a terminal myeloblastic crisis. The thio-TEPA failed to produce any significant alteration in the rapidly progressive, fatal course of the disease.

The remaining two patients showed rather marked improvement in the clinical and laboratory evidences of their disease following the administration of the drug. One 12-year-old boy died twenty-seven months after the onset of the disease. Death resulted from spontaneous rupture of the spleen during an acute myeloblastic crisis. The third patient was an 11-year-old girl who has been maintained free of symptoms for twenty months while receiving thio-TEPA. The course of her disease is described below:

P. H., white female, aged 11 years. This girl was first seen in September, 1952. She had had pain in the right hip for the past three weeks. There had been an eleven-pound weight loss. There were no other complaints, and on physical examination the significant findings were limited to severe pain in the right hip and marked limitation of motion. The patient showed evidence of recent weight loss and appeared chronically ill. The peripheral blood studies revealed the leukocyte count to be 360,000 per cubic millimeter with predominance of immature myelocytic forms. An aspiration biopsy of the bone marrow confirmed the diagnosis of subacute myelogenous leukemia.

A course of urethane was prescribed over the next twenty-six days with increasing doses up to 1.5 Gm. daily. This treatment failed to produce any alteration in the clinical or laboratory findings. On Nov. 4, 1952, she was given her first dose of thio-TEPA.

The clinical response to thio-TEPA therapy was excellent. Five days after the onset of therapy the pain in the right hip disappeared and nor-

TABLE I

CASE	AGE (YR.) SEX	DIAGNOSIS	PREVIOUS COURSE BEFORE THIO-TEPA			DURATION (WK.)	STATUS AT THE ONSET OF THIO-TEPA THERAPY					TOTAL DOSE (MG.)
			DURATION OF DISEASE (MO.)	PREVIOUS THERAPY	RESPONSE		PHYSICAL STATUS	SPLEEN, LIVER, NODES	HEMATOLOGICAL CONDITION			
									HB (GM.)	WBC × 1,000	PLAT. × 10,000	
1 M. B.	4 F	Acute leukemia	7	Aminopterin Cortisone	Clinical improvement	8	3	– – 1+	13.3	15	27	25
2 J. B.	2½ M	Acute lymphoblastic leukemia	3	Aminopterin Cortisone	Clinical improvement	4	2	3+ 2+ 2+	10	160	4	35
3 T. D.	3 M	Acute leukemia	10	X-ray	No improvement	–	1	3+ 2+ 3+	9.5	3	4.5	15
4 J. G.	4 M	Acute leukemia	3	Cortisone ACTH	Clinical improvement	4	2	3+ 3+ 1+	8.5	88	4	15
5 J. H.	9 F	Acute leukemia	13	ACTH	Clinical improvement	20	3	1+ 2+ 1+	7.3	13	14	13
6 L. L.	5 F	Acute leukemia	18	Aminopterin Amethopterin Cortisone	Complete revision	70	1	2+ 1+ 1+	7.2	2.7	9	25
7 T. L.	3¼ M	Acute leukemia	6	None	—	–	2	3+ 2+ 2+	60	10	4.6	15
8 D. M.	4 DM	Acute leukemia	8	Aminopterin Cortisone	Complete revision	20	2	3+ 2+ 2+	5.5	3.6	2	70
9 F. R.	2 M	Acute leukemia	1	None	—	–	2	1+ 1+ –	9.4	2.6	8	28
10 L. S.	5 M	Acute leukemia	3	Aminopterin	Clinical improvement	3	2	3+ 2+ 1+	11.5	3.5	16	95
11 J. P.	4 M	Acute leukemia	3	Aminopterin	Clinical improvement	2	1	3+ 2+ 3+	10.9	37	27	
12 A. M.	6 M	Acute leukemia	1	None	—	–	3	– – –	3.9	3.9	14	50
13 A. B.	8 F	Lymphosarcoma Acute lymphatic leukemia	18	X-ray Cortisone	No symptoms for the first 12 months. Some clinical improvement	8	1	2+ 1+ 2+	7.4	2	3.8	15
14 R. G.	10 M	Lymphosarcoma	2	None	—	–	3	Mediastinal mass Nodes 2+	12.6	5.3	40	27

I

THERAPY WITH THIO-TEPA				RESPONSE								
						HEMATOLOGICAL CONDITION						
TOTAL DOSE (MG.)	NO. OF DOSES	DURATION (DA.)	MODE OF ADMINISTRATION	PHYSICAL STATUS	SPLEEN, LIVER, NODES	HB (GM.)	WBC × 1,000	PLAT. × 10,000	DURATION (WK.)	SUBSEQUENT COURSE	CURRENT STATUS; WEEKS AFTER THIO-TEPA
25	5	6	IM	3	– – 1+	14	7.5	24	–	No response to therapy	On 6 MP
35	3	3	IM	2	3+ 2+ 1+	6.2	0.6	3	–	No response to therapy	Died; 1½
15	5	9	IM	2	2+ 1+ 2+	6.5	1.2	2	–	No response	Died; 1
15	5	5	IM	4	2+ 2+ –	6	1.8	2	3	Cortisone; Aminopterin; no response	Died; 10
13	3	3	IM	3	1+ 2+ 1+	7.5	4.0	3	–	No response	Died; 2
25	5	5	IM	1	2+ 1+ 1+	7.5	0.9	2	–	No response	Died during therapy
15	5	5	IM	1	3+ 2+ 2+	6.0	1.8	4.8	–	No response	Died 2 wk. after therapy was started
70	12	12	IM	3	2+ 1+ 1+	10	0.6	16	2	Some clinical improvement. Sepsis and death	Died; 3
28	14	19	IM	4	– – –	9	2.0	10	4	Aminopterin Complete remission	
95	15	15	IM	1	3+ 2+ 1+	5.6	0.6	2	–	No response	Died 3 wk. after therapy was started
			IM	4	2+ 1+ 2+	11	1.8	18	2	Clinical improvement	On therapy
50	10	10	IM	4	– – –	10	2.8	14	4	Marked clinical improvement. Asymptomatic	On therapy
15	3	3	IM	1	2+ 1+ 2+	7	2.0	3	–	No response to therapy	Died during therapy
27	7	7	IM	4	Mediastinal mass Nodes 2+	12.6	5.3	40			On therapy

TABLE I—

CASE	AGE (YR.) SEX	DIAGNOSIS	PREVIOUS COURSE BEFORE THIO-TEPA			DURATION (WK.)	STATUS AT THE ONSET OF THIO-TEPA THERAPY				
			DURATION OF DISEASE (MO.)	PREVIOUS THERAPY	RESPONSE		PHYSICAL STATUS	SPLEEN, LIVER, NODES	HEMATOLOGICAL CONDITION		
									HB (GM.)	WBC × 1,000	PLAT. × 10,000
15	7 M	Lymphosarcoma	1	None	—	–	2	Cervical mass Mediastinal mass	10	15	24
16 M. G.	5 M	Lymphosarcoma Acute lymphatic leukemia	1	None	—	–	2	Cervical Mediastinal mass	13.5	90	400
17	7	Lymphosarcoma Acute lymphatic leukemia	½	None	—	–	2	2+ 1+ Mediastinal mass	11.2	8.7	14
18 P. G.	4½ M	Subacute myelogenous leukemia	20	None	—	–	2	2+ 2+ 1+	7.0	35	2
19 P. H.	11 F	Subacute myelogenous leukemia	2	Urethane	No response	–	3	4+ – 1+	8.5	360	130
20 D. S.	11 M	Chronic myelogenous leukemia	25	Urethane	Clinical remission and hematological control	20	3	3+ – –	9.5	180	30
21 C. H.	12 M	Hodgkin's disease	½	None	—	–	3	Cervical mass Mediastinal mass	11	9.6	34

mal activity was resumed. She returned to a full school schedule, including play periods, in February of 1953; to date she has enjoyed completely normal activity. She visits the outpatient department one or two times weekly for the intramuscular injection of thio-TEPA. On one occasion an attempt was made to administer the medication orally. The leukocyte count increased rapidly until the dose had been increased to 20 mg. daily. At this dose the patient had episodes of gastric distress and vomiting. When the medication was again given parenterally, the leukocyte count dropped to lower levels of 12,000 to 16,000 per cubic millimeter. On two occasions when the dose was reduced to inadequate levels, the leukocyte count increased rapidly. When the dose was increased, there was a prompt fall in the total leukocyte count.

CONT'D

THERAPY WITH THIO-TEPA				RESPONSE							CURRENT STATUS; WEEKS AFTER THIO-TEPA
				PHYSICAL STATUS	SPLEEN, LIVER, NODES	HEMATOLOGICAL CONDITION			DURATION (WK.)	SUBSEQUENT COURSE	
TOTAL DOSE (MG.)	NO. OF DOSES	DURATION (DA.)	MODE OF ADMINISTRATION			HB (GM.)	WBC × 1,000	PLAT. × 10,000			
80	10	20	IM	4	Cervical mass reduced markedly Mediastinal mass reduced	10	1.8	19	3	HN_2; x-ray No response	Died; 4
240	35	94	IM and IV	1	Masses reduced markedly	10.0	1.6	92	4	X-ray therapy No response	Died; 2
60	10	10	IM	4	2+ 1+ Mediastinal mass	11.2	7.5	17	1	Marked clinical improvement. 10 da. of treatment	On therapy
86	14	14	IM	1	2+ 2+ 1+	6	2.3	2	–	No response	Died; 4
660	62	380	IM IV	4	– – –	13.4	15	90	12	Complete clinical remission and hematological control	On therapy
295	28	87	IM IV (10 mg.)	4	2+ – –	11	20	30	10	Acute myelogenic crisis during treatment. No response to big dose of thio-TEPA	Died 12 wk. with rupture of spleen
170	13	13	Oral	4	Cervical mass reduced in size Mediastinal mass unchanged	10.8	8.5	30	?	Patient lost for follow-up	

When last examined the patient was completely free of symptoms. The edge of the spleen was palpable 1.5 cm. below the costal margin.

Hodgkin's Disease.—The experience with Hodgkin's disease in children has been limited to one patient, although several adults with this disease were treated with thio-TEPA during the course of these observations. Oral medication was given in relatively large doses over a two-week period. The primary tumor mass in the neck and upper mediastinum was reduced in size, and the patient experienced no toxic effects from the drug. It was thought advisable to administer the material parenterally to further effect the course of the disease. Before such

a program of therapy could be instituted, the patient moved from the community and could no longer be treated.

COMMENT

The preliminary observations on the use of the thio derivative of triethylene phosphoramide would indicate that its usefulness clinically is in the same area as the other ethylenimine derivatives. The rapidly growing lymphomas such as lymphosarcoma and lymphoblastoma, which have not progressed sufficiently to interfere with the bone marrow function, respond most satisfactorily to these agents. Extensive clinical experience has shown that these agents do not exert a beneficial effect on the course of the acute leukemias. When other neoplastic processes which involve the marrow to a degree interfering with the adequate production of normal blood cells, little benefit is derived from the use of the drug. In such instances irreversible bone marrow failure accompanies the administration of these cytotoxic substances and appeared to lead to a fatal outcome. Early observations suggested that thio-TEPA might have a somewhat more easily controlled cytotoxic action than the ethylenimine compounds that have been previously available, and thus it might be useful in the control of acute leukemia. The experience recorded here would indicate that such is not the case and that thio-TEPA is contraindicated in the treatment of acute leukemias and in the acute leukemic phases of lymphosarcoma.

Our limited clinical experience with thio-TEPA would suggest that it has certain advantages over other agents used in the past in the management of patients with lymphosarcoma, Hodgkin's disease, and chronic leukemias. The drug appears to be much easier to manage in a wide variety of clinical situations than either nitrogen mustard or triethylene melamine, the two most commonly used ethylenimine derivatives. In several patients, definite antineoplastic action was evident with disappearance of leukocytosis, lymphadenopathy, and splenomegaly. During the same period there was an increase in production of erythrocytes and blood platelets with disappearance of anemia and thrombocytopenia. Such evidences of normal blood cell production during active therapy with an ethylenimine derivative have in the past been quite unusual. In addition, it would appear that thio-TEPA has been administered in this series of patients without producing significant degrees of bone marrow depression when a normally functioning hematopoietic organ was present at the onset of therapy. The predictability and comparative ease of controlling the toxic effects of this agent would appear to be a distinct advantage over ethylenimines that have been available up to this time.

Serious, and even fatal, toxic depression of the bone marrow may be readily produced by the injudicious use of this new agent. Thio-TEPA should be given only in situations where careful clinical and laboratory control of the patient is possible. During the early course of therapy this will usually necessitate daily hematological evaluation. The leukocyte count should not be allowed to go below levels of 3,500 to 4,500 per cubic millimeter. When the blood

count has been carefully controlled, other toxic manifestations resulting from thio-TEPA administration have not been encountered.

From the preliminary observations referred to in this report one might conclude that the thio derivative of triethylene phosphoramide can be a useful tool in the temporary management of certain of the malignant diseases arising in the hematopoietic and reticuloendothelial system. The effectiveness of the agent is dependent upon the proper selection of patients for its use and careful clinical and laboratory evaluations of the patient during the course of therapy. The toxic manifestations of poorly controlled therapy would appear to be limited to hematopoietic depression, which can be avoided by careful clinical and laboratory observation during the course of therapy.

Of the eighteen patients who died during the course of these observations, complete autopsies were performed in seventeen. A detailed report of these observations will be reported subsequently.

SUMMARY

1. The results of treatment with a thio derivative of triethylene phosphoramide of twenty-one children with leukemia, lymphosarcoma, and Hodgkin's disease have been presented.

2. This agent would appear to be of use in the temporary control of lymphosarcoma and chronic forms of leukemia.

3. The drug is contraindicated in the therapy of acute leukemias of childhood.

4. The toxic manifestations from overdosage of the agent have been limited to bone marrow depression. If this serious complication is to be avoided therapy must be guided by careful clinical and laboratory evaluation of the patients during the course of treatment.

5. This agent appears to have the advantage of a wider margin of safety between the toxic and therapeutic doses than do other ethylenimine derivatives currently available.

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SPLENOPORTAL VENOGRAPHY IN INFANCY AND CHILDHOOD

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DIRECT portal venography during laparotomy was the only method for visualizing the portal system before 1951, when Leger in Paris and Boulin in Belgium developed the percutaneous intrasplenic technique.

Since then, a few workers[1, 2, 3, 4, 6] have reported using the method on over ninety occasions. Their experience questions the success of the technique as an indispensable diagnostic means for most diseases involving the portal system. Though the value of the method could not be denied, it was felt that further study was needed before definite conclusions could be drawn.

TECHNIQUE OF PRESENT INVESTIGATION

Patients were prepared for radiography by fasting and by repeated soap enemas. Atropine and codeine were given one-quarter of an hour before venography, which was carried out under light general anesthesia with ethyl chloride and ether. With patients lying supine, a 2 mm. lumbar puncture needle was passed through the ninth, tenth, or eleventh space in the posterior axillary line, depending on the size of the spleen, then pushed medially, downward, and backward for some distance within the splenic pulp. Since respiratory excursions were deep and uncontrollable, the operator had to fix the spleen when palpable with his left hand, pushing it upward and backward toward the chest wall against the injecting right hand, in order to prevent tearing of the spleen during its up-and-down movement with respiration. Twelve to 20 c.c. of Ioduron 70 per cent (Cilag) was injected at a rate of 5 c.c. per second. Ioduron 30 per cent was used on few occasions, as was a mixture of the two in a 50 per cent solution. No differences were noted between the 70 and 50 per cent solutions except for some difficulty encountered during injection of the former solution. A 30 per cent solution gave an appreciably less distinct portal venogram, so that its use was discarded. The first film was taken after injecting three-fourths of the quantity, the second film just before completion, and the third, fourth, and fifth films were taken one, two, and three seconds after injection. A sixth film was taken as a routine thirty minutes later. Occasionally films were taken one hour and twenty-four hours after injection. Patients were kept under observation in bed for twenty-four hours.

SCHEME

We used this technique on thirty-three children, on whom forty-six portal venograms were made. Thirty-two venograms on twenty-four of the children were successful. Two of the children had a series of four successful venograms over a period of five

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months. Two others had two successful venograms in a period of two weeks. Cases were grouped as follows:

Group I: Comprised 8 normal children.

Group II: Comprised 17 patients with variable grades of liver cirrhosis; 9 of these were dietetic portal cirrhosis, 7 bilharzial periportal cirrhosis, and 1 a case of cirrhosis following infective hepatitis.

Group III: Comprised 8 patients with variable grades of splenomegaly without liver cirrhosis.

Fig. 1.—Normal splenoportal venogram. Case. 1.

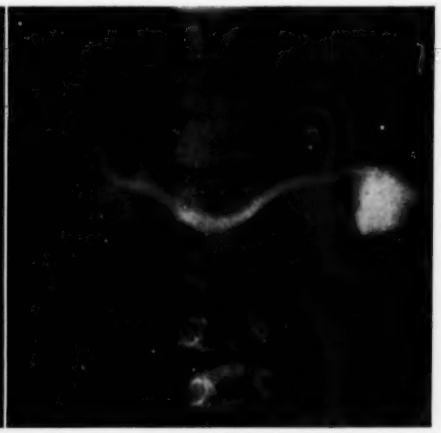

Fig. 2.—Normal splenoportal venogram. Case 3.

RESULTS

The splenoportal venogram reveals distinct patterns which were arbitrarily divided into four grades.

Grade 1: The portal venogram shows dilatation and tortuosity of the splenic vein without filling of collaterals.

Grade 2: One or more splenic collaterals become evident, i.e., short gastric, left gastroepiploic, and inferior mesenteric veins.

Grade 3: Splenic collaterals show an increase in density and one or more portal collaterals appear (left and right gastric veins and superior mesenteric vein with right gastroepiploic vein).

Grade 4: Splenic and portal collaterals show an increase in density with arrest of the dye in the portal or the splenic vein, the hepatogram failing to visualize.

Group I.—Of the eight normal children, a successful venogram was obtained in three (Table I). Failure in normal cases was due to the fact that the operator, unable to palpate the spleen, had to limit himself to its anatomical relations during injection, and, further, that, not easily feeling a normal splenic capsule, he was not at ease in pushing the needle in order to hit near the hilum.

In a normal splenoportal venogram, the splenic vein appeared of variable caliber and length, running a straight course or at most showing a single gentle undulation touching the lower border of the first lumbar vertebra (Figs. 1 and 2). The portal vein also depicted a variable size running a

TABLE I. SUMMARY OF FINDINGS

NO.	AGE (YR.)	SEX	DIAGNOSIS	CLINICAL					SPLENOGRAM		
				LIVER	SPLEEN	EVIDENCE OF PORTAL HYPERTENSION	LIVER BIOPSY	LIVER FUNCTION	BLOTCH	REFLUX	RADICLES
1	7	M	Normal	–	–	–	–	–	3 × 2 cm.²	Subcapsular minimum	3
3	10	M	Normal	–	–	–	–	–	3.5 × 3.5	Subcapsular minimum	2
6	12	F	Normal	–	–	–	–	–	10 × 4	Subcapsular minimum	2

S.M.V., Superior mesenteric vein. P.V., Portal vein.

straight course, forming an angle of about 45 degrees with the middle line. Its intrahepatic branches showed for some distance. The right branch and its ramifications filled faster than the left. No splenic or portal collaterals filled. Dilution of the dye along the portal vein by the superior mesenteric blood stream was at times evident, together with a small filling defect at the point of junction of the two veins. No similar dilution effect was noted at the site of entry of other splenic or portal tributaries (Figs. 1 and 2).

Group II.—This group included seventeen patients with variable grades of liver cirrhosis. Portal venography was successful in fifteen cases. Liver biopsy was done in all except one. The cases were classified pathologically as follows:

A. One case (No. 13), dietetic precirrhotic stage.

B. Four cases in the *early cirrhotic* stage:
Cases 9 and 19, bilharzial periportal cirrhosis.
Cases 16 and 22, dietetic portal cirrhosis.

C. Three cases of *established liver cirrhosis:*
Case 11, bilharzial periportal cirrhosis.
Cases 20 and 23, dietetic portal cirrhosis.

D. Seven cases of *advanced liver cirrhosis:*
Cases 10, 18, and 24, dietetic portal cirrhosis.
Cases 14, 17, and 21, bilharzial periportal.
Case 25, clinically advanced cirrhosis. (No biopsy was taken from this case.)

Liver function tests revealed impaired function in nine cases in the series.

Splenoportal venogram in these cases revealed:

A. One case (16) was normal.
B. Two cases (11 and 22) Grade 1 (Fig. 3).
C. Two cases (9 and 19) Grade 2 (Fig. 4).
D. Eight cases (10, 13, 14, 18, 20, 21, 23, and 24) Grade 3 (Figs. 5 and 6).
E. Two cases (17 and 25) Grade 4 (Fig. 7).

(See Table II)

The venogram of Case 18 of advanced dietetic portal cirrhosis showed

IN GROUP I, "NORMAL CHILDREN"

SPLENIC VENOGRAM				PORTAL VENOGRAM						
LENGTH AND CALIBER	COURSE	STREAM-LINING	COL-LAT-ERALS	LENGTH AND CALIBER	ANGLE	DILUTION BY S.M.V.	STREAM-LINING	COL-LAT-ERALS	HEPATOGRAM	GRADE
7.5 × 0.3 0.4 cm.	Straight	–	–	4.5 × 0.6 cm.	45°	+ and a small filling defect	–	–	Right P.V. showing main and medium branches. Left P.V. only a short stump	Normal
8 × 0.6	Gentle curve	–	–	3 × 0.7	45°	–	–	–	Right and left P.V. branches show main, medium, and small well-visualized ramifications	Normal
6.5 × 0.8	Gentle curve	–	–	4 × 1	45°	+ and a small filling defect	–	–	Right P.V. shows main, medium, and small ramifications. Left P.V. only a short stump	Normal

a thin, straight splenic vein despite the presence of several splenic and portal collaterals, indicating a high degree of intrahepatic obstruction (Fig. 8).

Case 17 of advanced bilharzial periportal cirrhosis revealed a dense homogeneous opacity of 4 by 10 cm. with an irregular outline, overlapping the first lumbar vertebra along the course of the splenic vein, with arrest of the dye in the portal vein. This was apparently due to portal thrombosis with marked dilatation of splenic vein and its collaterals (Fig. 9).

Case 25 of advanced liver cirrhosis showed a classical picture of thrombosis of portal and splenic veins. Venography in this case was repeated twice over a period of two weeks, revealing the same picture, with the inferior mesenteric and upper colic veins well visualized (Fig. 7).

Three patients with advanced bilharzial cirrhosis (Cases 14, 17, and 21) were successfully splenectomized. Portal manometry during operation revealed a pressure varying from 237 to 290 mm. saline. The paraumbilical vein was markedly dilated in all, and particularly in Case 14 in which splenic infarction was present.

Fig. 3.—Grade 1 splenoportal venogram in early dietetic liver cirrhosis. Case 22.

Correlation of the radiographic findings with the size of the spleen in Group II patients is shown in Table III.

It is apparent from Table III that there is no definite correlation between the size of the spleen and the grade of the venography, except in Grade 4

TABLE II. SUMMARY OF FINDINGS

NO.	AGE (YR.)	SEX	DIAGNOSIS	CLINICAL					SPLENOGRAM			LENGTH AND CALIBER
				LIVER	SPLEEN	EVIDENCE OF PORTAL HYPERTENSION	LIVER BIOPSY	LIVER FUNCTION	SPLENIC BLOTCH	REFLUX	RADICLES	
9	16	M	Bilharzial hepatosplenomegaly	2+	5+	–	Early bilharzial cirrhosis	Normal	2.8 × 1.5 cm.	Subcapsular and perisplenic	2	11.5 × 1.1 cm.
10	4	M	Dietetic liver cirrhosis	4+	2+	+	Advanced portal cirrhosis	Impaired	2 × 3	–	2	10 × 1
11	10	M	Bilharzial splenomegaly	2+	2+	–	Established bilharzial cirrhosis	Normal	4 × 3.5	Faint along needle track	2	8 × 1.0
13	10	M	? Dietetic liver cirrhosis	2+	1+	–	Cellular infiltration of portal tract	Normal	3 × 2	–	2	12 × 1.0
14	12	M	Bilharzial splenomegaly	1+	9+	P.P. 294 mm. saline, umbilical vein dilated	Advanced liver cirrhosis	Impaired	3 × 3	Very faint along needle track	2	13 × 1.3
16	6	M	Dietetic liver cirrhosis	6+	1+	±	Early portal cirrhosis	Normal	3 × 4	Moderate along needle track	2	8 × 0.4
17	13	F	Bilharzial hepatosplenomegaly	4+	7+	P.P. 237 mm. saline, umbilical vein 1.5 cm. diameter	Advanced liver cirrhosis	Impaired	3 × 3	Moderate subcapsular	1	7.5 × 1 ending in an opaque mass 10 × 4 cm.
18	1½	F	Dietetic liver cirrhosis	7+	Not palpable	++	Advanced liver cirrhosis	Impaired	2 × 3	Subcapsular	3	5 × 0.3
19	10	M	Bilharzial liver cirrhosis	2+	1+	–	Early bilharzial cirrhosis	Normal	3 × 2	–	1	11 × 1.0
20	4	F	Dietetic liver cirrhosis	6+	4+	++	Established portal cirrhosis	Impaired	4 × 2	–	2	10 × 1.0

IN GROUP II, "LIVER CIRRHOSIS"

SPLENIC VENOGRAM			PORTAL VENOGRAM						
COURSE	STREAM-LINING	COLLATERALS	LENGTH AND CALIBER	ANGLE	DILUTION BY S.M.V.	STREAM-LINING	COLLATERALS	HEPATOGRAM	GRADE
3 well-marked undulations	+	Short gastric veins	5.0 × 0.8 cm.	+	–	–	–	Short stump of both right and left portal vein branches	2
Steep curve downward and to right	+	Short gastric, lienorenal, gastrosplenic, subdiaphragmatic and I.M.V.	6.0 × 1.3	Horizontal course in line with Sp.Vn.	+	+	Right and left gastric veins, SM.V., and G.Ep.V.	Right and left P.V. Right showing up to small ramifications	3
3 well-formed curves	+	–	4.0 × 1.5	40	+	–	–	Left P.V. showing 4 cm. Right P.V. showing up to small ramifications	1
3 well-formed undulations	–	Short gastrics	3.0 × 1.5	75	+	–	Right and left gastric veins	Right and left P.V. shown as a faint blush	3
3 well-formed undulations	–	Short gastrics and I.M.V.	5.0 × 1.5	45	–	+ for a short distance along P.V.	Right and left gastric veins and right G.Ep. V.	Right P.V. showing medium ramifications. Left P.V. only a short stump	3
Straight and oblique downward and to right	–	–	6.0 × 1.3	60	Very mild	–	–	Short stump of both right and left P.V. branches	Normal
1 well-formed undulation	–	Short gastrics and I.M.V. reaching levels of 3rd Lb.V. and short collaterals spring from upper border of the mass	–	–	–	–	–	–	4
Straight and oblique downward and to right	–	Gastrosplenic and short gastrics	3.0 × 0.4	80	+	–	Right and left gastric veins and G.Ep.V.	Right P.V. showing up to small ramifications. Left P.V. not showing	3
Straight and oblique downward and to right	+	Short gastric and I.M.V.	4.5 × 1.0	50	+	–	–	Short stump of both right and left P.V. branches	2
1 well-formed undulation	+	Short gastrics and I.M.V.	4.0 × 1.0	65	+	+	Left gastric vein and S.M.V.	Right and left P.V. showing up to medium ramifications	3

TABLE II.—CONT'D

21	11	M	Bilharzial hepato-splenomegaly	3+	7+	P.P. 340 mm. saline	Advanced bilharzial cirrhosis	Impaired	3 × 1.5	Faint along needle track	2	10 × 1.5
22	11	M	? Dietetic liver cirrhosis	3+	5+	–	Early portal cirrhosis	Normal	4 × 2	Moderate along needle track	–	8 × 0.7
23	5	F	Dietetic liver cirrhosis	6+	6+	+	Established portal cirrhosis	Impaired	4.5 × 3	Moderate subcapsular	2	10 × 1.5
24	12	M	Bilharzial splenomegaly	3+	7+	Hematemesis +	Advanced bilharzial cirrhosis	Impaired	4 × 2	Moderate subcapsular	2	10 × 1
25	6	F	Postviral hepatitis liver cirrhosis	6+	6+	++	N.D.	Impaired ++	3 × 4	Moderate subcapsular	–	Shown for 2 cm.

P.P., Portal pressure. P.V., Portal vein. S.M.V., Superior mesenteric vein. I.M.V., Inferior mesenteric vein.
N.D., Not done. Lb.V., Lumbar vertebra. Sp.Vn., Splenic vein. G.Ep.V., Gastroepiploic vein.

Fig. 4.

Fig. 5.

Fig. 4.—Grade 2 splenoportal venogram in bilharzial liver cirrhosis. Note inferior mesenteric and short gastric veins. Case 19.

Fig. 5.—Grade 3 splenoportal venogram in advanced dietetic liver cirrhosis. Note splenic and portal vein collaterals. Case 10.

BLE II.—CONT'D

10 × 1.5	well-formed undulations	–	Short gastric and I.M.V. reaching 5th Lb.V.	4.0 × 1.5	60	+	–	S.M.V. very faintly shown	Faint short stump of right P.V.	3
8 × 0.7	One gentle undulation	+	–	3.0 × 1.0	45	–	–		Right P.V. showing up to small ramifications. Left P.V. only short stump	1
10 × 1.5	well-formed undulations	+	Lienorenal + 2 collaterals from distal part of Sp. Vn.	4.0 × 1.2	45	+	+	Very faint shadow of S.M.V.	Short stump of both right and left P.V. branches	3
10 × 1	well-formed undulations	+	Short gastrics and I.M.V.	5.0 × 1.5	40	+	–	Left gastric vein and S.M.V. faintly visualized	Faint blush around short stump of both right and left P.V. branches	3
Shown for 2 cm.	–	–	Gastrosplenic and short gastrics and I.M.V. with upper and middle colics shown	–	–	–	–	–	–	4

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Fig. 6.

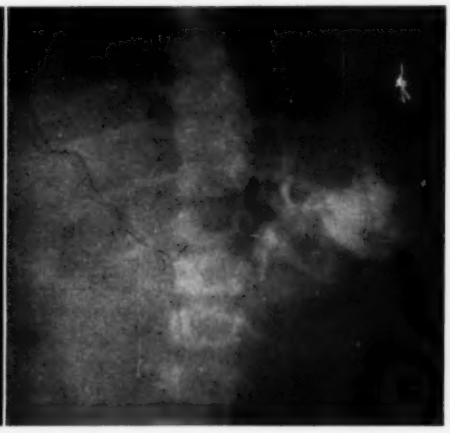

Fig. 7.

Fig. 6.—Grade 3 splenoportal venogram in advanced dietetic liver cirrhosis. Case 20.

Fig. 7.—Grade 4 splenoportal venogram in advanced postviral liver cirrhosis and portal vein thrombosis. Note inferior mesenteric with upper and middle colic veins. Case 25.

TABLE III

VENOGRAPHY GRADE	NUMBER OF CASES	SIZE OF SPLEEN		
		IMPALPABLE SPLEEN	SPLEEN +	SPLEEN ++
Normal	1	-	1	-
Grade 1	2	-	1	1
Grade 2	2	-	1	1
Grade 3	8	1	3	4
Grade 4	2	-	-	2

+ Spleen 1 to 4 fingerbreadths.
++ Spleen more than 4 fingerbreadths.

Fig. 8.

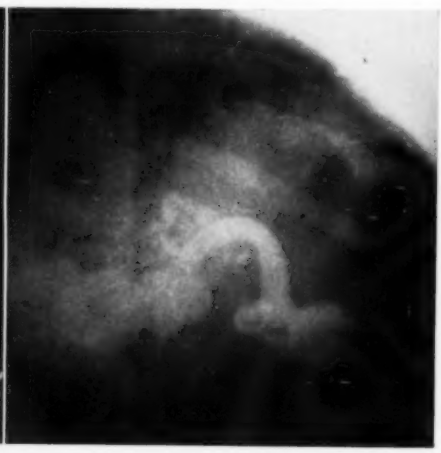

Fig. 9.

Fig. 8.—Grade 3 splenoportal venogram of Case 18, a 1½-year-old infant having dietetic liver cirrhosis.

Fig. 9.—Grade 4 splenoportal venogram in advanced bilharzial cirrhosis and portal vein thrombosis showing marked dilatation and tortuosity of splenic vein and its collaterals. Case 17.

TABLE IV

VENOGRAPHY GRADE	NUMBER OF CASES	LIVER BIOPSY			
		PRECIRRHOTIC STAGE	EARLY CIRRHOTIC STAGE	ESTABLISHED CIRRHOTIC STAGE	ADVANCED CIRRHOTIC STAGE
Normal	1	-	1	-	-
Grade 1	2	-	1	1	-
Grade 2	2	-	2	-	-
Grade 3	8	1	-	2	5
Grade 4	2	-	-	-	2

where portal or splenic thrombosis is present.

Table IV shows the relation between the grade of the venography and the pathological stage of the liver.

Table IV shows that all cases of advanced liver cirrhosis disclosed either Grade 3 or Grade 4 portal venography. All these cases showed either clinically detectable abdominal varicosity, or a

dilated paraumbilical vein was noted during splenectomy. One patient from the precirrhotic group revealed Grade 3 venography. Pathologically, this case showed dense cellular infiltration of the portal tracts which apparently caused the rise of the portal pressure.

Group III.—This group includes eight cases of variable grades of splenic enlargement due to different causes. None of these patients showed clinical evidence of portal hypertension (Table V). Successful venograms were obtained in six cases; three were cases of hemolytic anemia (28, 29, and 30), one a case of Banti's syndrome (31), and two were cases of obscure splenomegaly (26 and 33).

Splenoportal venograms of Cases 26, 28, 29, and 30 revealed variable grades of dilatation and tortuosity of the splenic vein (Grade 1) (Figs. 10 and 11) which were in direct proportion to the size of the spleen. There was no filling of any of the splenic or portal collaterals in the four cases. The last two cases of this group (Cases 31 and 33) revealed radiographic evidence of splenic vein thrombosis. In both cases the dye diffused through a large area of splenic pulp with filling of few splenic radicles; and Case 33, obscure splenomegaly, showed a few gastrolienal collaterals as well. Case 31 proved to be a patient with Banti's anemia and death occurred after a severe attack of hematemesis lasting three days.

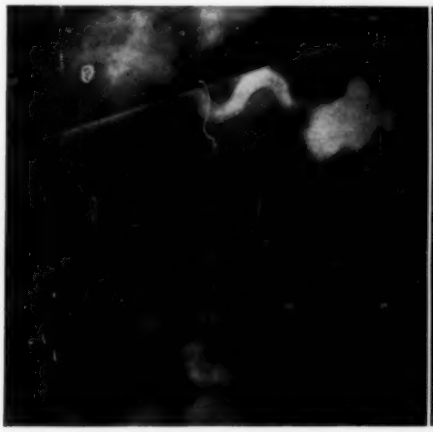

Fig. 10.

Fig. 11.

Fig. 10.—Grade 1 splenoportal venogram of Case 29, primary hypersplenism.
Fig. 11.—Grade 1 splenoportal venogram. Case 30.

COMPLICATIONS

In none of our cases was there any complication. A few patients complained of pain over the spleen during the first twenty-four hours after injection. One of these patients had splenic infarction. The injection should be performed only in a hospital to obviate any disaster that may result from rupture of the spleen, and should never be done in the presence of chronic infection, or a tendency to hemorrhagic diathesis.

TABLE V. SUMMARY OF FINDINGS IN GROUP II

NO.	AGE (YR.)	SEX	DIAGNOSIS	CLINICAL					SPLENOGRAM			LENGTH AND CALIBER
				SPLEEN	LIVER	EVIDENCE OF PORTAL HYPERTENSION	LIVER BIOPSY	LIVER FUNCTION	BLOTCH	REFLUX	RADICLES	
26	5	M	Rickets Splenomegaly	3.0+	2.0+	–	Normal	Normal	2.5 × 2 cm. + a splenic sector 3.5 × 6 cm.	Along needle track	–	× 0.8 cm
28	5	F	Chronic hemolytic anemia	3.0+	6.0+	–	–	Normal	4 × 2.5	Moderate subcapsular	2 draining lower most part of spleen	10 × 0.8
29	7	M	Primary hypersplenism	5.0+	1.5+	–	N.D.	Normal	6 × 4	Moderate subcapsular	1	10 × 0.8
30	2	M	Subacute hemolytic anemia	3.0+	2.0+	–	N.D.	Normal	3 × 3	Minimum along needle track	–	4 × 0.7
31	3	M	Splenic anemia Banti's syndrome	3.0+	2.0+	Hematemesis	Normal	Normal	6 × 4 increasing by direct spread to 11 × 5	–	2 with no filling of splenic vein	–
33	2	M	Obscure splenomegaly	3.5+	2.0+	–	N.D.	Normal	6 × 3 increasing to 8.5 × 4 by direct spread	Minimum along needle track	4 splenic radicles with no filling of splenic vein	–

DISCUSSION

Successful portal venography was found of practical value in assessing the degree of portal hypertension. Each of the four grades into which the venograms were classified infers a different degree of portal pressure.

The splenic vein in a normal splenoportal venogram does not show kinking or tortuosity. The statement made by Fuld and associates that tortuosity and kinking can be demonstrated in normal portal venograms due to mechanical push of the spleen during injection was not verified in any of our venograms on normal children. However, our injection was made in the posterior axillary line with patients lying supine, while Fuld used the scapular line with patients lying prone.

Grade 1 portal venogram shows dilatation and tortuosity with no filling of either splenic or portal collaterals. It occurs when there is augmented splenoportal circulation either due to an early degree of portal hypertension, or congestive splenomegaly without portal obstruction.

GROUP III, "SPLENOMEGALY WITHOUT LIVER CIRRHOSIS"

SPLENIC VENOGRAM				PORTAL VENOGRAM						
RADICLES	LENGTH AND CALIBER	COURSE	STREAM-LINING	COLLATERALS	LENGTH AND CALIBER	ANGLE	DILUTION BY S.M.V.	STREAM-LINING	COLLATERALS	HEPATOGRAM	GRADE
–	0.8 cm.	2 gentle undulations	–	–	3 × 1 cm.	50°	+ with a small filling defect	–	–	Both right and left P.V. well visualized but intensity of filling of right branch is more and filling up to small ramifications	1
2 draining lower most part of spleen	10 × 0.8	2 well-formed undulations	–	–	4 × 1.2	40°	+ with big filling defect	+	–	Both right and left P.V. well filled up to small ramifications	1
1	10 × 0.8	3 well-formed undulations	–	–	5 × 1	40°	+	–	–	Right P.V. filled up to small ramifications. Left P.V. shows a blush	1
–	4 × 0.7	1 gentle curve	–	–	6 × 0.8	40°	–	–	–	Right and left P.V. branches show a faint blush	1 (early)
2 with no filling of splenic vein	–	–	–	–	–	–	–	–	–	–	Splenic vein thrombosis
4 splenic radicles with no filling of splenic vein	–	–	–	Gastro-splenic	–	–	–	–	–	–??	Splenic vein thrombosis

Grade 2 portal venogram shows filling of splenic collaterals. Short gastric veins were found to fill earlier than the inferior mesenteric vein in the present series.

Grade 3 portal venogram shows filling of portal collaterals with increased density in the splenic collaterals. All advanced cases of liver cirrhosis unassociated with portal or splenic thrombosis belonged to this grade. The intensity of filling of collaterals was found to be proportionate to the degree of portal obstruction.

Grade 4 portal venogram shows arrest of the dye along the portal or splenic vein due to portal, or portal and splenic, thrombosis, with complete reversal of the portal circulation through short gastric veins, superior and inferior mesenteric veins, lienorenal and lienogastric veins, subdiaphragmatic, esophageal, intercostal, and retroperitoneal veins.

The following observations are worthy of comment:

Portal Venogram.—

1. Dilution of the contrast medium at the site of entry of superior mesen-

teric vein was present in 80 per cent of cases that showed both portal and splenic veins. No correlation could be detected between the degree of dilution and the grade of portal venogram.

2. The visualization of two blood streams in the portal vein; the superior mesenteric blood stream, and the dye-containing splenic stream when evident was only so along the proximal part of the portal vein, the dye perfusing both its right and left branches. This fact denies the theory of streamlining in human liver (Figs. 12 and 13).

3. Greater filling of the right portal branch than the left was noted in most of our cases. This might be due to the bigger size of the right branch which is also more in line with the main portal blood stream.

4. A feature of all our splenoportal venograms is the direction of the portal vein which runs somewhat more horizontal than usually depicted in anatomical diagrams. Most cases that revealed extreme degree of horizontal position in the present series belonged to high grades of portal venography.

Splenic Venogram.—

1. The degree of dilatation and tortuosity of splenic vein is in direct proportion to the size of spleen. The splenic vein was unduly narrow and straight in Case 18, an 18-month-old infant in whom the spleen was not palpable despite intense abdominal varicosities and advanced liver cirrhosis. Whether the umbilical vein forms an efficient anastomotic channel that comes to work easily in this age group remains a possibility that has to be investigated. However, demonstration of the umbilical vein radiographically was not possible in any of our cases, even in those that revealed a markedly dilated umbilical vein during sple-

Fig. 12.

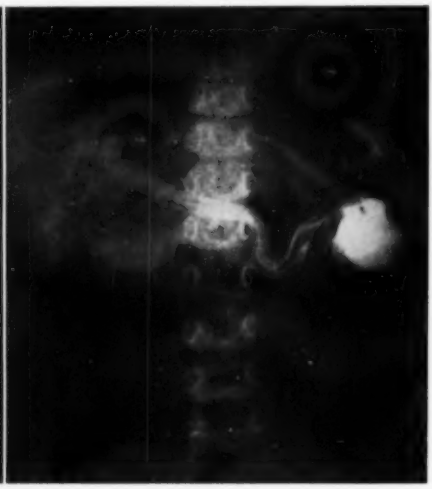

Fig. 13.

Fig. 12.—Splenoportal venogram disclosing two blood streams in the portal vein (splenic and superior mesenteric). The splenic stream perfusing both right and left branches of the portal vein.

Fig. 13.—Splenoportal venogram demonstrating streamlining along the proximal half of the portal vein.

nectomy. Apparently the dye never reached the vein with sufficient speed to cast a radiographic shadow.

2. Kinking and tortuosity of splenic vein, when demonstrated, was found to be a constant finding whether the films were taken during injection or after withdrawal of the needle. Even in cases that were repeated four times, the splenoportal venogram revealed the same pattern on the four occasions; hence, mechanical push of the spleen by the needle cannot be a factor in its production.

3. Streamlining of blood carried to splenic vein by different splenic radicles was sometimes present for a variable distance along the splenic vein but hardly extends to the portal vein (Fig. 13). Whether the circulation within the spleen is open, semiopen, or closed, and whether it works in distinct compartments or not cannot be deduced to any extent of certainty from splenoportal venography.

4. In few cases, moderate subcapsular or perisplenic reflux of the contrast medium along the puncture tract occurred. The degree of this reflux depends on varying factors: the proximity of the dye to a main splenic radicle, the rate and force of injection of the dye, and the potency of the splenoportal circulation.

Hepatogram.—To visualize a distinct hepatogram through percutaneous splenic venography is not always possible, and necessitates a uniformly rapid rate of dye injection or else the blood stream will be damped beyond the portal vein and misinterpretation with intrahepatic portal obstruction is a liability. The intensity of the hepatogram seems to depend, to a great extent, on mechanical factors.

Serial exposures are imperative if we are to avoid errors in interpreting the findings in splenoportal venography. One film may show the head of the contrast medium while it may be normal or the obstruction may be hepatic or posthepatic.

Value of Splenoportal Venography.—

1. Splenic venography has proved of practical value for assessing the degree of portal hypertension.

2. It is the only means for localizing the site of obstruction in the splenoportal circulation and for gauging the size of both splenic and portal veins. For this reason it is a valuable preoperative measure in cases of portal hypertension where splenorenal or a portacaval anastomosis may be needed. It also can be used as an easy postoperative means to detect potency of a portacaval anastomosis.

3. Splenic venography has thus fulfilled much that was desired for clinical diagnosis of many cases of obscure splenomegaly and hematemesis.

SUMMARY

Forty-six splenoportal venograms were done on thirty-three infants and children. Cases are classified into three groups. Results in each group are discussed. The technique used is described. Possible practical applications for the method are enumerated.

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CLINICAL AND SEROLOGICAL EXPERIENCES IN TREATING HEMOLYTIC DISEASE OF THE NEWBORN

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SINCE 1947 we have collaborated in the diagnosis and in the treatment of 243 cases of hemolytic disease of the newborn by means of replacement transfusion. During this period certain investigations have been carried out and some clinical observations made which we believe should be emphasized and documented.

From our experience derived from treating patients with erythroblastosis before and since the advent of replacement transfusion, we are of the opinion that most cases of hemolytic disease of the newborn, except the very mild ones and the moribund cases, should be treated by replacement transfusion. We have learned that it is hazardous to do a replacement on a child who has extreme dyspnea from severe atelectasis or other obstructive lesions. This must be carefully differentiated from dyspnea due to cardiac failure in severe cases of erythroblastosis in which carefully done replacement transfusions can be lifesaving. It must be thoroughly understood that, at times, apparently mild cases can change, and in a few hours show that they are severely affected. We must be ready and willing to change our evaluation of such a case. For this reason all patients must be carefully watched so that proper treatment can be instituted at the *earliest* possible moment. Premature infants with erythroblastosis are more susceptible to kernicterus than full-term infants. Because of this, they should be given the benefit of early replacement as soon as a diagnosis is made, even though the signs and symptoms are not marked. In handling premature infants, any cell sensitization is serious. Previous history may give a lead to early treatment.

With few exceptions it is not considered advisable to deliver a baby early by induction, thus adding prematurity with its peculiar susceptibility to kernicterus to the hazards of erythroblastosis. Occasionally, when there is a bad history of a mother's inability to carry a live baby to term, an early induction should be considered, but not before the thirty-eighth week.

In hemolytic disease of the newborn the diagnosis and prognosis are not made from any one or two signs or symptoms, but from the observation and careful evaluation of the case in toto, using all the criteria available. This includes family history, meticulous serology, hematology, and complete physical examination. Cell sensitization tests are valuable in diagnosis and as an indication for treatment. Antibody estimations are important, but can be misleading. We

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have occasionally seen severe cases with low antibody and also mild cases with high antibody reports. Bilirubin estimations are of definite value in diagnosis, prognosis, and follow-up, particularly because it is now recognized that clinical jaundice and serum bilirubin do not always run parallel. Clinical jaundice usually lags behind bilirubin estimations, and our concern in preventing kernicterus is paramount. All these facts have been previously pointed out.[1, 2]

In cases of hemolytic disease of the newborn we use the Coombs test and a test devised by Witebsky, Rubin, Engasser, and Blum[3] in determining infant cell sensitization. Recently the latter test has been modified[4] by the introduction of serum-albumin mixture as the diluent. This modified test recommends itself because of its simplicity and sensitivity, also because of its added value in ABO cases. We believe this test should be used more generally.*

Because this test has not been described in pediatric literature, we are giving a more or less detailed description at this time. The baby's cells are suspended on a slide over an illuminated viewing box in three different diluents: (1) in a drop consisting of one part of normal adult human serum and two parts of 30 per cent bovine albumin, (2) in a drop of normal human adult AB serum, (3) in a drop of saline solution. As a further control, normal cells are set up parallel to the sensitized baby's cells. A heavy blood cell suspension of unwashed cells should be used. By means of wooden applicators, cells are transferred from the blood clots into the drops of the different diluents until a rather heavy suspension is obtained. Or, we sometimes suspend the cells under investigation in a small amount of its own serum (about a 50 per cent suspension) and then transfer a small drop of this suspension into the drops of different diluents on the slide. Because the baby's cells are usually sensitized by incomplete antibodies, spontaneous agglutination of the sensitized cells occurs as soon as these cells come in contact with the suitable diluent, which is normal AB serum or a serum-albumin mixture. In our hands, this test has proved as reliable as the direct Coombs test, and identical results are obtained in most instances when both tests are performed simultaneously. According to the experience of one of us,[4] the examination of the baby's sensitized cells in different diluents can also be of differential diagnostic significance, as shown in the following experiment.

Two babies suffering from hemolytic anemia of the newborn were delivered within a few hours on the same day: Case 1, Baby Po, blood group O, Rh positive, whose mother belonged to blood group O, Rh negative (cde/cde) and whose father belonged to blood group O, Rh positive, subtype Rh_2 (cDE/ce); Case 2, Baby Ni, blood group A, Rh positive, whose mother was blood group O, Rh positive, subtype Rh_1 (CDe/ce), and whose father belonged to blood group A_1, Rh positive, subtype Rh_1Rh_2 (CDE/c). The results obtained in testing for sensitization of the babies' cells after observing the reaction on a warm stage for twelve minutes are recorded in Table I. Baby Po's cells were strongly agglutinated when suspended in serum-albumin, and were somewhat weaker

*These investigations were carried out at the Buffalo General Hospital, Department of Bacteriology and Immunology.

but still definitely agglutinated in normal serum. The Coombs test also was strongly positive. This was a typical case caused by Rh sensitization. In contrast, Baby Ni's cells were strongly agglutinated in normal adult serum but only faintly, if at all, in the serum-albumin mixture (±). The Coombs test also was very weak and questionable in this case. There was no indication of Rh sensitization in the second baby (Ni), nor could any other factor known to us be blamed for this sensitization with the exception of the AO incompatibility.

erator for a few days, the results could become vitiated.

These findings are interesting both from the theoretical and from the practical points of view. From the practical point of view, they lead the way for the correct interpretation and diagnosis of the kind of incompatibility involved. From the theoretical standpoint, they call attention to the fact that the type of antibody responsible for Rh sensitization differs from that involved in ABO sensitization so far as the basic protein molecule is concerned with which the antibody

TABLE I. DETERMINATION OF SENSITIZATION OF BABY'S CELLS USING DIFFERENT DILUENTS

	BABY PO	BABY NI	BABY SH (NORMAL CONTROL)
AB serum + albumin	++++	±	—
AB serum	+++	+++(+)	—
Saline solution	—	—	—
Antihuman serum Antiserum (rabbit) Coombs test	++++	±	—

According to our experience, the difference in the degree of agglutination caused by normal serum as a diluent on the one hand, and serum-albumin mixture on the other, as shown in these two cases, is a characteristic one. Cells sensitized by an Rh antibody are usually more quickly and more strongly agglutinated in serum-albumin mixture than in normal serum; this is in contrast to cells sensitized by an antibody belonging to the ABO system, which are more strongly and more quickly agglutinated in normal serum than in the serum-albumin mixture. The Coombs test is characteristically absent or weaker in ABO incompatibilities than in Rh incompatibilities. It is important for both serological and clinical reasons that tests for sensitization of baby's cells be carried out as soon as possible. If the baby's sensitized cells were kept in the refrig-

function is associated. Occasionally cases are seen clinically suggestive of ABO incompatibilities whose blood cells are only weakly agglutinated or not agglutinated at all. This test, based upon the spontaneous agglutination of sensitized cells in proper diluents, should prove to be of value in cases of isosensitization, not only in Rh and ABO incompatibilities, but in other incompatibilities such as Kell and "s," etc., provided the sensitizing antibody as produced in the mother is demonstrable by the use of the respective diluents. It is hoped that still better diluents may be found which will further improve the practical validity of the test under discussion. We believe that the test based on the spontaneous agglutination of sensitized cells in different diluents is the most valuable method of confirming

the diagnosis of hemolytic disease of the newborn. This is doubly true when the condition is due to ABO incompatibility. Other laboratory procedures such as determining the presence of spherocytosis, the percentage of reticulocytes, and the osmotic fragility of the red cells are of less diagnostic value.

The direct Coombs test, on the other hand, will prove superior to the test just described in cases of iso-sensitization due to antibodies in the mother's serum demonstrable only by the indirect Coombs technique and not by the diluents in present use.

We are of the opinion that cases due to ABO sensitization should be evaluated, and treated in the same manner as the Rh cases,[5, 6] depending on the severity. We realize that there are more mild cases in the ABO group, and many infants of heterospecific pregnancies have neither signs nor symptoms of hemolytic disease, but we have also seen some very severe cases. Kernicterus and stillbirths have been reported in ABO sensitization.[7] Physiological jaundice has recently been placed in a similar category in the causation of kernicterus as cases of iso-immunization (hemolytic disease). The severe cases with high bilirubin levels,[8] marked symptoms, and dire results can hardly be called physiological, but could be designated *pathological hepatic jaundice of the newborn.* These cases, occurring in premature and some full-term newborn infants, are probably due to liver inefficiency.

In order to save these children from kernicterus and brain damage, some specific indications for treatment by exchange transfusion will have to be worked out. Bilirubin blood estimations should be of value. Many of the deaths and neurological sequelae of premature infants could conceivably come from hyperbilirubinemia. Infants so affected could probably be benefited by timely replacement transfusion.

Since 1947 we have made serial examinations of many infants' bloods during replacement transfusions; this was briefly reported.[3] Later however, we learned that a serum-albumin mixture is a much better diluent to demonstrate Rh sensitization than normal adult human serum alone. The following experiment illustrates the superiority of the serum-albumin mixture over adult serum as a diluent. Every second specimen taken during the replacement was collected in separate test tubes. Altogether, thirteen specimens were received in the laboratory. The blood cells from alternate specimens, namely, the first, third, fifth, seventh, eleventh, and thirteenth specimens, were suspended on a slide in one drop each of (1) serum-albumin mixture, (2) normal adult serum, (3) anti-D diagnostic serum, (4) saline solution. The resulting agglutinations are shown in Table II. As can be seen from this experiment, the baby's blood cells taken during different stages of the exchange transfusion were agglutinated up to the ninth specimen, in both the serum-albumin mixture and the diagnostic anti-D serum, and only to the fifth specimen in normal adult serum (provided the ± agglutination is considered negative). The experiment shows that the baby's cells are not only more strongly agglutinated in serum-albumin, but that this diluent is more sensitive than normal adult serum. These results can be considered typical. However, some cases were encountered where agglutination of the baby's sen-

sitized cells could be observed only in the first two or three specimens, indicating the limitation of this technique for the evaluation of the extent of replacement. The direct Coombs test can occasionally give positive results even with the blood cells from the last specimen obtained during exchange transfusion. Apparently a smaller percentage of sensitized cells in a mixture of normal donor's cells and the baby's cells is sufficient to cause agglutination upon addition of the Coombs reagent than upon the addition of normal diluents (serum or serum-albumin mixture).

It is interesting to note that the agglutination of the sensitized baby's Rh-positive cells by the diagnostic anti-D serum (Table II), seemed to run practically parallel with the agglutination in the serum-albumin mixture. Agglutination of sensitized cells by specific antisera should therefore be interpreted with reserve regarding its specific nature, because normal serum, and especially serum-albumin mixtures, also might induce agglutination. Consequently the serological analyses of sensitized cells should be weighed with great caution unless the cells are suspended in saline solution and saline agglutinins used for test sera, and, even then, the results might not always be considered reliable.

We take great care in the selection of donor's blood used for exchange transfusion. Obviously, it should be as fresh as possible, both from the standpoint of cell survival and serum electrolytes. A special problem is presented in the selection of suitable blood for ABO incompatibilities. In these cases we use O blood (irrespective of the Rh type), and add at least 1 or 2 vials of AB substances to a pint of blood. If there is time, we titrate the iso-agglutinin content of several O bloods and select that O blood with the lowest anti-A or anti-B titer (depending upon whether it is an A or B incompatibility). AB substances are then added to the O blood selected, to further reduce the iso-agglutinin content, thus preventing additional damage to the baby's sensitized cells by transfusion of incompatible iso-agglutinins. We do not use A blood in incompatibilities to the A factor for the same reason that we do not use Rh-positive blood in incompatibilities due to the Rh factor. The selection of donor's blood is equally important in incompatibilities caused by the formation of anti-e antibodies in homozygous Rh_1 mothers (C-C). In such cases a donor's blood should be chosen which is homozygous for C, and thus does not contain the e factor.

TABLE II. DETECTION OF SENSITIZED BABY'S CELLS DURING DIFFERENT STAGES OF EXCHANGE TRANSFUSION

BABY KARL, BLOOD GROUP O, RH POSITIVE

	NORMAL CONTROL CELLS RH POS.	NORMAL CONTROL CELLS RH NEG.	PATIENT'S CELLS NO. 1	NO. 3	NO. 5	NO. 7	NO. 9	NO. 11	NO. 13
Serum-albumin mixture	—	—	++++	+++	++	++	++	±	±
Normal adult serum	—	—	++	+	+	±	±	—	—
Anti-D diagnostic serum	++++	—	++++	+++	++	++	+	±	±
Saline solution	—	—	—	—	—	—	—	—	—

In our series we have found no statistical differences in the use of blood from male or female donors.

Bilirubin is a very important factor in the development of kernicterus.[9, 10] Unlike the above findings, bilirubin estimations do not tell the true story of what has been accomplished by replacement transfusion in reducing the total body bilirubin, and thus minimizing the chances and dangers of kernicterus. Some who do not use replacement transfusion in the treatment of hemolytic disease of the newborn have quoted bilirubin estimations and especially the secondary rise in serum bilirubin in endeavoring to prove the uselessness of replacement transfusion in reducing bilirubin. This discrepancy is undoubtedly due to the rapid redistribution of bilirubin in the body after its removal by replacement transfusion and its reappearance in the blood. Added to this is bilirubin released by continued hemolysis of Rh-positive cells by the antibodies remaining after an 80 per cent blood replacement. Hyperbilirubinemia depends on the degree or severity of hemolysis plus the ability or inability of the liver to excrete bilirubin. It is only logical to assume that the amount removed must be of definite value in recovery, and in the prevention of kernicterus with resulting brain damage.

Fig. 1 illustrates bilirubin estimations in typical cases when a single replacement transfusion is done. Repeated replacement transfusions, a second or even a third or fourth time, have been advocated to keep the serum bilirubin under 20 mg. per cent. We occasionally resort to this procedure, but believe that the early successful completion of a 500 c.c. exchange with fresh blood in good condition will obviate the necessity of multiple replacements in the majority of cases. We realize that bilirubin estimations are of great importance in deciding

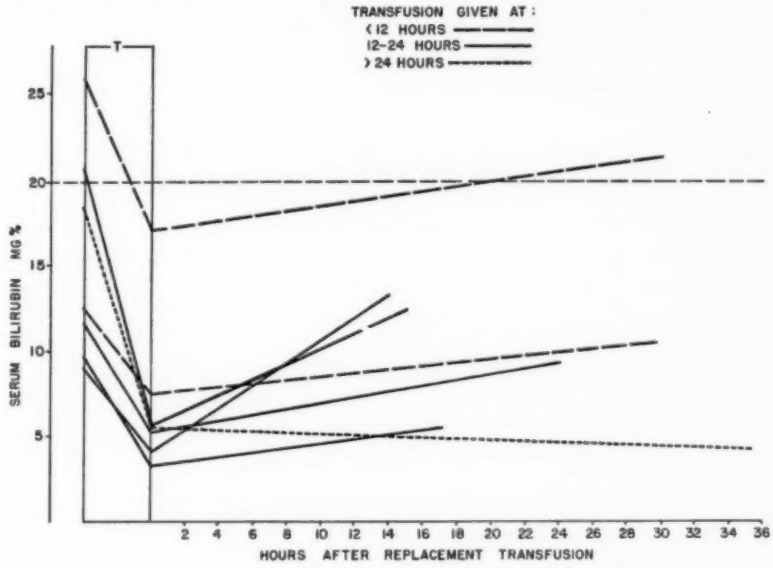

Fig. 1.

whether or not to do multiple replacements in order to prevent kernicterus.

Fig. 2 depicts bilirubin estimations during the course of treatment by multiple replacement transfusions. Occasionally during replacement in the severely affected cases the child's condition may cause concern: heart or respiratory failure can occur. The replacement should then be slowed or temporarily stopped for a few minutes, and the baby observed and stimulated; checked. When elevated beyond physiological levels (60 mm. of water), a sufficient deficit should be established to keep the venous pressure within normal range; this is to prevent untoward results due to heart failure and pulmonary congestion.

At times there is severe disease without low hemoglobin; these patients certainly do not need a blood increment.

Sometimes it is necessary to terminate the replacement short of 500 c.c.; then, if deemed necessary, another replacement can be done, depending on

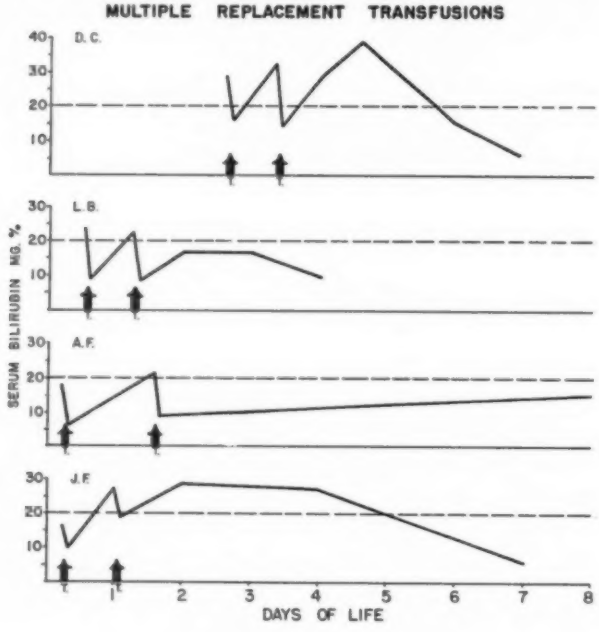

Fig. 2.

suction and oxygen should be used. Attention should be given to the need for proper amounts of calcium to prevent tetany; it should be given slowly, carefully watching for reaction such as dangerous bradycardia. The venous pressure should be taken before starting the replacement transfusion, and should be periodically the condition of the child and the bilirubin estimations. In case of anemia following replacement transfusion, a simple transfusion of Rh-negative cells resuspended in saline solution can be given. Using judgment in all of these details determines the success or failure in the treatment by replacement transfusion.

Statistics have abundantly proved the value of properly conducted replacement transfusion in reducing the mortality and morbidity in hemolytic disease of the newborn. Our statistics are shown in Table III. The first two years (1947-1948) we reported[11] twenty-six replacements with a loss of five patients, mortality rate 19.2 per cent. During that time we received bad cases and late cases. At post mortem it was found that one patient died from hemolysis from giving overheated blood, one from massive cerebral hemorrhage, one had congenital heart disease. From 1949 to date we have had references in increasing numbers, most of which have been referred to us earlier. During the last six years we have done 240 replacements on 217 patients, with a mortality rate of 2.5 per cent. Our morbidity appears low; we know of only one case of kernicterus. Probably with a careful neurological survey, some sequelae would be found; such a follow-up should be made. However, at least half of our cases have remained under our personal supervision; we find these patients free from neurological abnormalities.

A survey of one hundred erythroblastotic infants and children up to 5 years of age was done and reported[12] from the Children's Hospital, Los Angeles, and the Department of Pediatrics, University of Southern California, School of Medicine. It is difficult to evaluate their report, for nothing was said about the type of treatment these babies received; the only illustrative case history quoted, Case No. 43711, was an infant with a late diagnosis and "treated with multiple small transfusions of Rh-negative sedimented cells."

We wish to restate that we believe early diagnosis and treatment by replacement transfusion will lower the death rate in erythroblastosis and keep the neurological sequelae to a minimum. We use one of two methods in doing replacement transfusions, either the umbilical method[1] or the saphenous method.[13] We elected to use the saphenous method in ninety-four instances. Sometimes the umbilical vein is difficult to cannulate; occasionally it is impossible; at times the cord is too short, or it is not in good condition. We see no reason for going to extremes in endeavoring to revive a dried up, mum-

TABLE III

YEAR	NUMBER OF CASES	NUMBER OF REPLACEMENTS	UMBILICAL	SAPHENOUS	MULTIPLE	DEATHS	MORTALITY
1947	10	10	4	6		2	19.2%
1948	16	16	9	7		3	
1949	20	20	14	6		1	2.5%
1950	21	21	10	11		2	
1951	38	40	22	18	2	1	
1952	40	40	33	7	0	0	
1953	42	48	35	13	6	1	
1954*	56	71	45	26	12	1	
Total	243	266	172	94	20	11	

These replacement transfusions were done by Drs. Douglas P. Arnold, Kenneth M. Alford, and George H. Selkirk.

Most of the replacement transfusions were done at the Buffalo Children's Hospital and the Millard Fillmore Hospital.

Many of the routine clinical serological examinations were done at the Serological and Bacteriological Laboratory of the Buffalo Children's Hospital under the direction of Dr. Erwin Neter.

*Total up to Sept. 1, 1954.

mified, or clotted umbilical cord or vein when a neat, clean, easy, alternate route is available. It is sometimes easier to cannulate the saphenous vein than it is the tortuous umbilical vein. We use the same technique as originally described for the saphenous transfusion.[13] We have never had to discontinue a saphenous vein transfusion because of technical difficulties.

We recommend the saphenous vein method for all second or third replacements. Clots form in the umbilical vein and although an attempt is made to suck them out, it is quite possible to push them into the circulation. If they are infected, this could result in blood stream infection or in infected emboli lodging in the lung.

We find the saphenous vein method of replacement transfusion just as satisfactory as the umbilical vein method, and with a little experience the technique is as easy to perform. Our reason for this emphasis and reiteration is because in two recent surveys on hemolytic disease of the newborn[14, 15] the saphenous vein replacement transfusion was not even mentioned. We believe this method should be called the saphenous method, and not the femoral[16]; the femoral vein is not touched; it is merely used as a passageway as is the iliac and the vena cava. Such a designation might lead to the erroneous idea that the femoral vein is opened, and possibly tied. Such a procedure is not dangerous, but it is not desirable and should not be used. We have never seen any lymphedema from tying the saphenous vein high in the groin, and the vein is much more easily located in the position previously described by us. If the directions[13] are carefully followed, there will be no difficulty in successfully completing a saphenous vein transfusion. Before incising the vein, we apply ether on a compress to prevent retraction when cut. A slight bevel on the No. 19 catheter* will aid in its introduction. The distal end of the vein is not tied until the transfusion is completed[17]; the catheter, size 19, is lightly tied into the proximal end so that it will not come out prematurely, but not so tightly that the position cannot be changed during the procedure. Both ends of the vein can be ligated when the transfusion is finished. A cocoon dressing or some type of a collodion spray (Aeroplast) is used to seal the incision. This will prevent contamination from excreta.

We now use Tuohy adapters instead of needles and glass in making connections. We wish to reaffirm our previous views that replacement transfusion is at present the only satisfactory method for treating most cases of clinical hemolytic disease of the newborn, and restate our admonition *"When in doubt replace."*

An example in point:

Baby P., full-term, weight 7 pounds, was born by caesarean section because an ovarian cyst was complicating delivery. The mother had one previous child, 3½ years old, Rh positive, and well since birth. No other pregnancies, and no transfusions. The serological history revealed: mother, Group A, Rh negative (cde/cde), at delivery showed Rh antibodies of medium high titer; father, Group B, homozygous, Rh_1 (CDe/CDe); baby, blood Group O, Rh positive.

At birth the baby appeared normal and showed no signs of erythroblastosis except the cells were strongly sensitized as shown by positive Witebsky-Rubin and Coombs tests. There were no erythroblasts in the blood smear.

*Clay-Adams Catalog Number PE 90.

This report should have led us to do a replacement transfusion for it has been our experience that babies with strongly sensitized cells should be considered as seriously affected even though other signs are lacking. The baby was carefully observed several times a day. In twenty-four hours it showed slight jaundice, and had a serum bilirubin of 7.6 mg.; in forty-eight hours it was 17 mg., and on the third day the bilirubin had risen to 22 mg. per cent, which is an estimation which causes apprehension concerning the development of kernicterus. We also believe in endeavoring to keep the bilirubin under 20 mg. per cent. On the fourth day the bilirubin started to fall (14 mg. per cent). The course is indicated in Fig. 3. During these days the only change in the child's condition was a gradually deepening jaundice. The hemoglobin never went below 16 grams, nor the red count below five million. The spleen and liver remained not palpable. The child showed neither neurological signs nor symptoms, and, to date, appears perfectly normal.

In spite of this fortunate outcome we believe this child should have been "replaced." It would have saved days of worry, and recrimination had the child developed kernicterus. In other words, we believe a physician treating clinical hemolytic disease of the newborn cannot guess the outcome, and is not being clever in "just getting by" without a replacement transfusion.

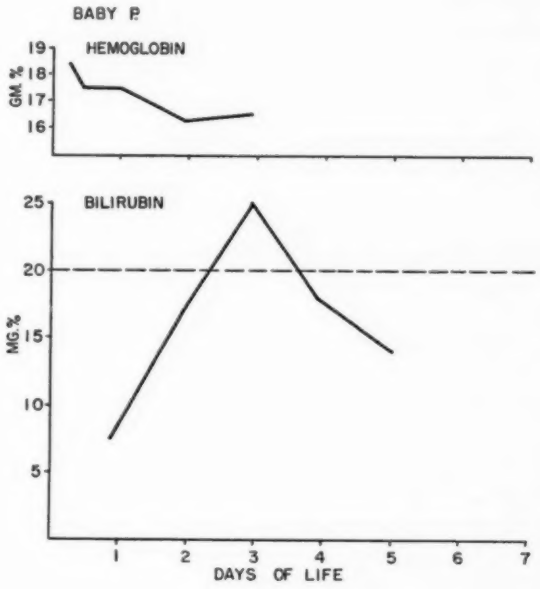

Fig. 3.

The hazards of replacement transfusion properly done are slight, and the results eminently more satisfactory than looking back on a case which was not done, but should have been. Such a case cannot be recalled, and can result in death or, what is worse, a case of kernicterus.

SUMMARY

1. We have presented statistics with the results of the treatment by replacement transfusion of 243 cases of hemolytic disease of the newborn.

2. A test has been described based upon the agglutination of baby's sensitized cells in different diluents, as applied in the diagnosis of hemolytic disease of the newborn due to Rh and ABO incompatibility.

3. We have again emphasized the use of the saphenous vein method for replacement transfusion.

4. We have suggested that replacement transfusion may be of value in the treatment of certain cases of severe pathological hepatic jaundice of the newborn, other than those associated with blood incompatibilities.

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THE USE OF CORTISONE IN THE TREATMENT OF RETICULOENDOTHELIOSIS

Cases From the Pediatric Service of the Valley Forge Army Hospital, Phoenixville, Pa.

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IN RECENT years there has been a renewed interest in the reticuloendothelioses for two reasons. First, the theory has been advanced and accepted by the majority of clinicians and pathologists that eosinophilic granuloma, Hand-Schüller-Christian syndrome, and Letterer-Siwe's disease are not only related but are probably different stages in a single disease process. Second, new methods of therapy have been tried with varying degrees of success. The purpose of this paper is to report on the use of cortisone in each of the three forms of reticuloendotheliosis.

Generalized treatment of the reticuloendothelioses has consisted mainly of roentgen-ray therapy, antibiotics, antifolic acid compounds, nitrogen mustards, and, recently, cortisone and corticotropin. In addition, symptomatic measure such as iron and blood transfusions have been given without significantly affecting the course of the disease. In conditions like reticuloendotheliosis where the symptomatology and prognosis are so varied, it is difficult to properly evaluate any therapeutic regime.

X-ray therapy usually promptly heals the lesions in eosinophilic granuloma, favorably (but frequently temporarily) affects the bony lesions and symptoms of diabetes insipidus in Hand-Schüller-Christian syndrome, and has no significant effect on Letterer-Siwe's disease. Surgical excision, and sometimes just a simple biopsy, also quickly cures eosinophilic granuloma lesions.

Bierman and associates[1] achieved clinical improvement using various antibiotics in twins with Letterer-Siwe's disease, but these results have not been duplicated by other workers.[2, 3, Case 3] Antifolic acid compounds may at times be of some benefit in Hand-Schüller-Christian syndrome but are of no value in Letterer-Siwe's disease. Blattner[4] reported temporary improvement after nitrogen mustard therapy in six cases, but in only one was there regression of the pathologic process. Low fat and low cholesterol diets have no value in any of the reticuloendothelioses.

In 1951 Blahd and co-workers[5] first reported on the equivocal effect of cortisone in an adult with Hand-Schüller-Christian syndrome. Since then, Karlen,[2] Cox,[6] and Sewell[7] reported single cases in which cortisone was effective in either Hand-Schüller-Christian syndrome or Letterer-Siwe's disease. Bass and associates[8] reported on five cases of reticuloendotheliosis treated with cortisone and/or corticotropin. Two of these children had complete disappearance of signs and symptoms, one had sustained improvement, one had temporary improvement

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but then went downhill and died despite antifolic acid drugs and cortisone, and the fifth patient, an infant with Letterer-Siwe's disease, died despite large doses of corticotropin. During this same period of time, Gray and Taylor,[9] Henderson and Thompson,[10] and Keizer and Rochat,[11] reported on single cases of reticuloendotheliosis that were unaffected by corticotropin.

In the three cases reported here, cortisone appeared to have beneficial effect in each instance. However, the improvement was short-lived in Cases 1 and 3 (eosinophilic granuloma and Letterer-Siwe's disease), and despite cortisone treatment, a fatal outcome was not prevented in the patient with Letterer-Siwe's disease (Case 3). In Case 2 (Hand-Schüller-Christian syndrome), the patient has remained well since treatment, but has been maintained on a low daily dosage of cortisone.

Although cortisone is not the solution to the treatment of reticuloendotheliosis, it should be included in the therapeutic armamentarium of this disease for the following reasons:

1. It has been shown[12] that cortisone depresses the reticuloendothelial system as indicated by its phagocytosis and its regenerative capacity.

2. Adrenocortical hormone plays a role in fat metabolism. In this disease lipid metabolism is affected secondarily.

3. Cortisone has been of value in other diseases involving the reticuloendothelial system.

4. Cortisone seems to be the most efficacious drug yet uncovered for the treatment of reticuloendotheliosis.

CASE REPORTS

CASE 1.—In November, 1953, J. J., a white female aged 2 years 3 months, first developed intermittent mild generalized abdominal pain and headaches. One month later an ulceration was noticed on the left side of the hard palate which caused some irritability and slight pain on eating. On Jan. 12, 1954, physical examination revealed only a 10 mm. circumscribed, fairly clean ulcer of the mucous membrane of the hard palate extending medially and posteriorly from the left upper molar teeth. The hemoglobin was 10.5 grams per cent, red blood count 5,410,000 per cubic millimeter, and mouth and skull x-rays were negative. A biopsy of the lesion showed

Fig. 1.—Showing tumorous soft tissue swelling in the left parotid region. Case 1.

stratified squamous epithelium with some acanthosis and an underlying infiltration of mononuclear cells and was diagnosed as chronic inflammatory reaction. Treatment with penicillin and streptomycin for one week produced slight improvement, but slight irritability and mild pain on eating continued. The child was admitted to Rodriguez Army Hospital, Puerto Rico, on March 18, 1954, where a repeat biopsy was considered fairly typical of eosinophilic granuloma.

In April, 1954, a painless swelling of the soft tissues over the left parotid area was noted. Repeat skull x-rays then demonstrated a 2 cm., irregular,

round area of rarefaction in the left temporal bone, an erosion of the left zygomatic arch, and the soft tissue swelling. X-rays of the chest and long bones were negative. Terramycin was given orally for one week with no effect on the preauricular swelling.

and roughly circular about 2½ inches in diameter. It was not attached to the skin above or to the underlying muscle or bone. An anemia was present, and ferrous sulfate therapy was started. A skeletal survey showed the original lesions plus involvement of

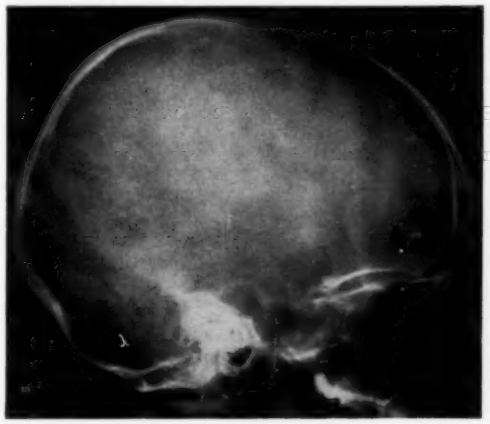

Fig. 2.—X-ray of skull showing the punched-out bony defects. Case 1.

Fig. 3.—X-ray of the skull showing destruction of the left zygomatic arch. Case 1.

On May 5, 1954, she was transferred to the Valley Forge Army Hospital, asymptomatic and with no change in physical findings. The mass over the left parotid area was indurated, nonfluctuant, slightly tender,

the squamosa of the left temporal bone and the lateral wall of the antrum. From May 12 to 24, 1954, the patient received roentgen-ray therapy consisting of 1,000 r divided into ten doses of 100 r each, administered through

a single 7 by 7 cm. portal centered over the sella turcica. By the time of discharge from the hospital on May 24, both the palatal ulcer and the soft tissue swelling had shown definite improvement, and by May 31 the ulcer was completely healed and the swelling gone.

The patient was asymptomatic until June 8, when pain in the mouth on eating developed plus "toothaches" at night. At that time ulcers on the right and the left upper gums and hard palate were noted similar in appearance to the original lesion. Also x-rays showed bone erosion around the upper molars, plus the other skull defects. An examination on July 8, because of an upper respiratory infection, disclosed another ulceration on the lower right gingiva. The respiratory infection responded promptly to Terramycin, but the ulcers did not. On July 22 she was readmitted to Valley Forge Army Hospital with many ulcerations of the upper and lower gums and hard palate mainly on the lingual side. Surrounding each ulcer was an area of erythema, and around the upper right and left second molars there was recession of gum tissue. The oral lesions were biopsied and again reported as eosinophilic granuloma. X-rays showed almost complete healing of the previous skull defects, and the anemia had not been improved by iron medication.

On July 29 oral cortisone 50 mg. daily was started and increased to 100 mg. daily on July 31. By July 31 there had been great improvement. The ulcers were present, but the erythema was completely gone. The improvement continued, and the appetite increased progressively to voracious. The weight gradually increased from 28 to 32½ pounds, although no edema was found. A moon face and protuberant abdomen developed and disappeared later when the cortisone dosage was lowered. The blood pressure remained normal. The hemoglobin rose to 11.2 grams per cent. The mouth ulcers completely cleared by August 29, but considerable permanent recession of gum tissue was present around the roots of the upper (left more than right) second molars and a lesser amount around the lower first and second molars on the right. The patient was discharged on Sept. 2, 1954, on 12.5 mg. of cortisone daily. Despite the cortisone, new lesions appeared in the mouth in the latter part of September, 1954. Increasing the dosage of cortisone to 25 mg. daily had no effect on these lesions, and cortisone was discontinued on Nov. 3, 1954.

Fig. 4.—Showing the massive cervical lymphadenopathy. Case 2.

CASE 2.—This white female, L. G., a full-term infant, was well until 10½ months of age, when cough, irritability, and rhinorrhea developed. After these symptoms had persisted for a month, a physician was consulted. Examination revealed a husky infant with good color, cough, irritability, and rhinorrhea. Symptomatic treatment was of no benefit, and one week later a purulent conjunctivitis and anterior cervical lymphadenopathy developed. Hemoglobin was 9.5 grams per cent, and Fer-in-Sol was started. On Dec. 21, 1953 (one week later), fever, bilateral otitis media, and enlarged preauricular nodes appeared, and penicillin was given for four days. By December 30 a posterior cervical lymphadenopathy had developed, and a chest x-ray showed a bilateral enlargement of the

hilar nodes. Terramycin for five days was of no avail.

This child was hospitalized on Jan. 5, 1954. Laboratory studies, including a skeletal survey and bone marrow aspiration, were normal except for anemia and the enlarged hilar nodes. A cervical lymph node biopsy was diagnosed as Letterer-Siwe's disease. During this hospitalization she had a fair appetite, low-grade fever, and stable weight, and received one transfusion. The patient was transferred to another Army hospital on January 20, and remained there until March 15. Her fever disappeared, and a small area of rarefaction developed in the left ischium. Fer-in-Sol did not improve the anemia but was continued on discharge.

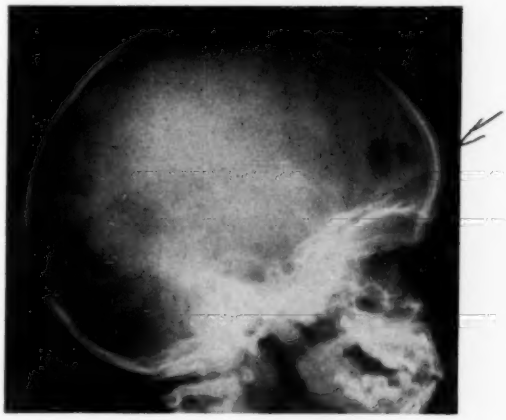

Fig. 5.—X-ray of the skull showing the punched-out bony defects. Case 2.

Beginning in mid-April there was steady enlargement of the cervical nodes, excessive drowsiness, and about two weeks later weakness in both legs. In mid-May tenderness in the buttocks appeared. On June 18, 1954, rapid enlargement of the left side of the neck began and practically doubled in size overnight, accompanied by pain, tenderness, and an increase in respiratory rate. She was readmitted to the hospital on June 21, 1954, with fever, pallor, irritability, poor appetite, and massive bilateral cervical lymphadenopathy. Laboratory examinations were negative except for the persistent anemia, slight eosinophilia in the bone marrow study and x-ray changes of small, irregular, punched-out areas of rarefaction in the skull bones and the distal end of the right tenth rib, as well as enlargement of the similar lesion in the left ischium. The hilar lymph nodes had also increased in size. While taking a biopsy of the tenth rib on July 1, a small pneumothorax occurred and was treated by aspiration. This biopsy and one from a cervical node were reported as Letterer-Siwe's disease. This child received penicillin and streptomycin for nine days postoperatively.

On July 14 this patient was transferred to the Valley Forge Army Hospital. Clinically, she had not changed. The hemoglobin was 7.4 grams per cent, x-rays showed the enlarged mediastinal nodes and bigger defects in the skull, ischium, and rib. On July 23 cortisone, 50 mg. daily, was started, and on July 25 the dose was increased to 100 mg. daily. Almost immediately the child felt better, ate better (and later developed a voracious appetite), was pleasanter, and was generally improved. The cervical nodes got progressively softer and smaller. The hemoglobin rose to 12.4 grams per cent

on August 23, and the iron was discontinued. (The patient had received iron medication since December, 1953, without effect on the anemia.) The child gradually gained weight from 28 to 32¼ pounds, although no edema was found. The blood pressure remained normal. A marked moon face and protuberant abdomen developed while on cortisone which later disappeared when the dosage was lowered. X-rays showed a decrease in the size of the hilar nodes and the lesions in the ischium and the rib, and all the bone lesions showed evidence of regeneration and healing. The cortisone dosage was lowered in a step-wise manner from 100 mg. daily on Aug. 20, 1954, to 12.5 mg. daily on Sept. 10, 1954. This patient will be maintained on this latter dosage. By the time of discharge from the hospital (end of September, 1954), a new bony defect appeared in the right parietal region, but all the other bony defects were smaller and showed evidence of continued healing.

Fig. 6.—X-ray showing the bony defects in the right tenth rib (distal) and left ischium, and enlargement of the mediastinal lymph nodes. Case 2.

This case demonstrates the similar pathologic picture in the reticuloendothelioses. Although repeated biopsies were diagnosed as Letterer-Siwe's disease, clinically this case belongs in the category of Hand-Schüller-Christian syndrome with possibly early transitional changes to the acute form.

CASE 3.—D. W. was a full-term white female born on Aug. 14, 1950. About June 1, 1951, she developed a hacking cough which cleared in a few days but was followed by a postauricular lymphadenopathy. She was treated with sulfadiazine for one week, at which time "tiny red dots" were noted on the chest and axillae, and the cough recurred.

On June 11, 1951, she was admitted to the Valley Forge Army Hospital, appearing chronically ill with moderate hepatomegaly, marked splenomegaly, slight postauricular lymphadenopathy, and slight drainage from the left ear. The significant laboratory studies were hemoglobin 7.3 grams per cent, red blood count 2,300,000 per cubic millimeter, and negative x-rays. A cervical lymph node biopsy was reported as compatible with Letterer-Siwe's disease. Three blood transfusions were given, and on July 13 penicillin, chloramphenicol, and oral cortisone (50 mg. daily) were started with prompt and marked clinical improvement. By August 21 the hepatomegaly, lymphadenopathy, and drainage from the left ear had disappeared, the anemia had improved, and the spleen had decreased in size; and so all medication was stopped. She was discharged from the hospital on August 27, 1951, and was well for three weeks. Then irritability developed, followed by discharge from both ears. The patient

was treated with chloramphenicol for one week with no improvement.

On September 26, 1951, this patient was readmitted to the hospital, again looking chronically ill and having irritability, low-grade fever, a thin drainage from both ears, mucoid nasal discharge, no hepatomegaly, slight splenomegaly, slight cervical lymphadenopathy, and induration about both mastoids. Pertinent laboratory data then revealed hemoglobin 9.0 grams per cent, red blood count 3,100,000 per cubic millimeter, hemolytic *staphylococcus aureus* in the drainage from both ears (sensitive only to Aureomycin and terramycin), no aeration of mastoids on x-ray (normal for this age), and increased markings in the right base on chest x-ray. She was started on penicillin and sulfadiazine and given a transfusion. Although both ear drums were pale and not bulging, a bilateral myringotomy was done on September 29, but no pus was obtained. Because of sensitivity studies, aureomycin replaced the other antibiotics. The patient's condition continued to deteriorate, with the anemia progressive, but a bone survey showing no bone lesions. On October 18, a bilateral mastoidectomy was performed and another transfusion given. The downhill course and drainage from both ears continued despite these measures and also x-ray treatment of the mastoid regions. On November 14, with a red blood count of 2,580,000 per cubic millimeter and hemoglobin of 7.2 grams per cent, aureomycin was discontinued, another transfusion given, and cortisone was started orally, 100 mg. daily. Cortisone was decreased to 50 mg. on November 20 and then to 25 mg. daily on December 8. On December 13 the ear discharge became foul-smelling due to a proteus organism (found on culture), and painful, tender, bleeding gums were first noted. Streptomycin was started but had no effect and was discontinued on Jan. 7, 1952. Cortisone was increased to 50 mg. daily. Despite repeated transfusions, other courses of penicillin, and the cortisone, the downhill course continued with progressive drainage from both ears, pallor, anorexia, anemia, weakness, loss of weight, and splenomegaly; and the successive appearance of x-ray evidence of decreased density of the mandible with marked loss of bone especially along the right alveolar ridge; several punched-out radiolucent areas in the skull; a soft, bulging tumor in the frontal region; spiking temperature; petechial eruption on the

Fig. 7.—X-ray of the skull showing the punched-out bony defects. Case 3.

abdomen and the neck, later becoming purpuric; extrusion of teeth; generalized edema; and a thick, yellowish, oleaginous, crusted rash of the scalp. Terminally, hemoglobin was 2.3 grams per cent, twitchings and coma developed, and the patient died on April 30, 1952.

The histologic appearances of sections of the cervical lymph node and of the skin lesion obtained by biopsies during the life of the patient were compatible with Letterer-Siwe's disease. The tissue obtained from the left ear was diagnosed pathologically as subacute inflammatory reaction. At autopsy, histologic evidence of Letterer-Siwe's disease was found involving the lungs, spleen, thymus, the submucosa of the entire gastrointestinal tract, the skull, the bone marrow (diffusely), the skin (trunk, neck, and scalp), and all the lymph nodes.

SUMMARY

The various types of therapy employed in reticuloendotheliosis are briefly discussed, and the rationale for the use of cortisone is presented. The effect of cortisone on three patients, representing each of the three stages of reticuloendotheliosis, is reported. Cortisone produced only transient clinical improvement in eosinophilic granuloma and Letterer-Siwe's disease and did not prevent a fatal outcome in the latter case. The patient with Hand-Schüller-Christian syndrome has been well since treatment with cortisone.

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INFLUENCE OF TYPE OF FEEDING ON pH OF STOOL, pH OF SKIN, AND INCIDENCE OF PERIANAL DERMATITIS IN THE NEWBORN INFANT

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PERIANAL dermatitis of the newborn infant can frequently be seen in hospital nurseries. It is an irritation of the skin immediately about the anus, varying up to 4 cm. in diameter, erythematous, and frequently exudative. Severe disease is characterized by multiple small superficial ulcerations, while mild disease may often be missed unless the buttocks are manually separated. Perianal dermatitis is not to be confused with diaper rash, which occurs later and affects the convex surfaces of the thighs and buttocks and the pubic region, and is generally believed to be caused by ammoniacal urine.[1]

The frequency of perianal dermatitis among artificially fed infants has been shown to be higher than among the breast-fed infants.[2] The substitution of lactose for vegetable carbohydrate in the formula has lowered the incidence significantly. It has been postulated that this difference may be due to a variation in stool pH. To determine the effect of various feedings on pH of the stool and of the skin, and on the relation of pH of the stool to incidence of perianal dermatitis, examinations were made on a total of 251 newborn infants.

CLINICAL MATERIAL AND METHODS

All infants in this study were between 2 and 9 days of age except four; these were 11, 12, 14, and 30 days old, respectively. After the first day, during which only water was given, they were distributed among three feeding groups.

One hundred forty infants were breast-fed, fifty were fed a prepared formula approximating human milk, and sixty-one were fed an evaporated cow's milk and maltose-dextrin formula. In each group, approximately half the babies were white and half were Negro. The proportions of these formulas and their caloric strengths for the age periods studied are shown in Table I.

It was considered desirable to examine the effects of feedings in general use for comparison with breast milk. Similac was chosen as representative of the prepared formulas approximating breast milk in composition, and because it contains lactose as the sole carbohydrate. The evaporated cow's milk and maltose-dextrin formula, in the proportions used here, is a frequently encountered stock formula.

TECHNIQUE OF THE STUDY

The pH of the stool, of the perianal skin, and of the axillary skin was measured, and the incidence of perianal dermatitis noted. A Beckman model G pH meter was used for pH determination. It was equipped with the Beckman glass electrode type 42,

This work was done in the Maternity Nursery of Cooper Hospital with the cooperation of Dr. George B. German, obstetrician, and Dr. Vincent Del Duca, pediatrician.

especially designed for use on impenetrable surfaces such as skin.

The stools were tested by applying the electrode to the fecal matter adhering to the perianal skin. This area was then cleansed thoroughly with water and dried with cotton sponges, and the electrode applied to the perianal skin approximately 1 cm. from the anus. The axillary skin pH was determined at a point about 3 cm. below the peak of the axilla.

anal skin observations in Tables II and III show fewer infants than the other two columns.

As might be expected, during the first three days of life while the infants were passing meconium, there was little variation in the mean pH of the stool, perianal skin, or axillary skin, whatever the feeding. The mean and range of pH values for the first three days of life are shown in Table II.

TABLE I. PROPORTIONS AND CALORIC VALUES OF ARTIFICIAL FEEDINGS

FEEDING	2ND AND 3RD DAYS	4TH AND 5TH DAYS	6TH DAY +
Simulated human milk	Similac powder* 25.5 Gm. H_2O 360 ml. Calories per fl. oz. 10.7	Similac powder 51 Gm. H_2O 540 ml. Calories per fl. oz. 14.5	Smiilac powder 76.5 Gm. H_2O 720 ml. Calories per fl. oz. 16.3
Evaporated cow's milk + maltose-dextrin formula	Evaporated milk 90 ml. H_2O 450 ml. Dextri-Maltose No. 1 15 ml. Calories per fl. oz. 8.75	Evaporated milk 135 ml. H_2O 400 ml. Dextri-Maltose No. 1 23 ml. Calories per fl. oz. 13.25	Evaporated milk 150 ml. H_2O 385 ml. Dextri-Maltose No. 1 30 ml. Calories per fl. oz. 15.2

*Similac powder supplied by M & R Laboratories, Columbus, Ohio.

RESULTS

The data were tabulated according to race, age, and type of feeding, and analyzed statistically.[3] There was found to be no significant racial difference and, accordingly, the data for white and Negro groups have been combined except in the tabulation of incidence of perianal dermatitis. Although comparative incidence among Negro and white infants was not statistically significant because of the smallness of the sample, the ratio of incidence corroborated the difference demonstrated in an earlier study.[2]

Since inflamed or denuded skin gives a more alkaline determination than normal skin, the readings of perianal skin pH for cases of perianal dermatitis were not included in the tabulations. Consequently the peri-

From the fourth day on, the mean axillary skin pH values for all feedings become more acid, although there is little difference from one feeding to another. Stool and perianal skin pH values show divergences for the different feedings. The mean and range of pH values from the fourth day are shown in Table III.

Comparison of the data in Tables II and III shows that with increased age the drop in stool pH is greatest for the breast-fed infants and least for the infants on the evaporated cow's milk and maltose-dextrin formula. Stool pH of infants on simulated human milk drops to a level close to that of those on breast milk.

The mean perianal skin pH for breast-fed infants decreases, for simulated human milk-fed infants remains

unchanged, while that of the infants fed evaporated milk and maltose-dextrin shows an increase.

The stool pH values for the infants who were on their respective feedings the longest, those 6 days of age and older, generally show even greater divergence from the values of the first three days of life. For the breast-fed infants in this age group the mean value is 5.4, for those fed simulated human milk 5.7, and for those on

TABLE II. STOOL, PERIANAL SKIN, AND AXILLARY SKIN pH OF BABIES ONE TO THREE DAYS OLD, ON VARIOUS FEEDINGS

	STOOL			PERIANAL SKIN			AXILLARY SKIN		
	NO. OF	pH		NO. OF	pH		NO. OF	pH	
FEEDINGS	INFANTS	MEAN	RANGE	INFANTS	MEAN	RANGE	INFANTS	MEAN	RANGE
Breast milk	69	6.4	4.4-8.6	67	5.8	4.8-7.6	69	6.0	4.7-7.3
Simulated human milk	16	6.1	4.7-7.0	15	5.7	5.1-6.3	16	5.9	4.5-6.7
Cow's milk, M-D formula	31	6.3	5.1-8.0	28	5.8	5.0-7.0	31	5.9	5.0-6.8

TABLE III. STOOL, PERIANAL SKIN, AND AXILLARY SKIN pH OF BABIES FOUR DAYS OF AGE AND OLDER, ON VARIOUS FEEDINGS

	STOOL				PERIANAL SKIN				AXILLA		
	NO. OF	pH			NO. OF	pH			NO. OF	pH	
FEEDING	INFANTS	MEAN	RANGE	*	INFANTS	MEAN	RANGE	*	INFANTS	MEAN	RANGE
Breast milk	71	5.7	4.4-7.6	5.5-5.9	63	5.4	4.3-7.3	5.3-5.5	71	5.6	4.5-6.6
Simulated human milk	34	5.8	4.9-7.0	5.6-6.0	28	5.7	4.8-6.6	5.5-5.9	34	5.3	4.0-6.3
Cow's milk, M-D formula	30	6.2	4.7-7.7	6.0-6.4	21	6.0	5.3-6.8	5.8-6.2	30	5.5	4.3-6.5

*Calculated possible range of theoretically true mean.

TABLE IV. INCIDENCE AND SEVERITY OF PERIANAL DERMATITIS ON VARIOUS FEEDINGS

	NO. OF	CASES OF DERMATITIS			PER CENT WITH
FEEDING	INFANTS	SEVERE	MILD	TRACE	DERMATITIS
Breast milk	140	2	4	4	7.1
Simulated human milk	50	1	4	2	14.0
Cow's milk M-D formula	61	2	10	0	19.7

TABLE V. INCIDENCE AND RACIAL DISTRIBUTION OF PERIANAL DERMATITIS ON VARIOUS FEEDINGS

	WHITE INFANTS			NEGRO INFANTS		
FEEDING	NO. OF INFANTS	CASES OF DERMATITIS	PER CENT WITH DERMATITIS	NO. OF INFANTS	CASES OF DERMATITIS	PER CENT WITH DERMATITIS
Breast milk	65	5	7.7	75	5	6.7
Simulated human milk	29	3	10.3	21	4	19.0
Cow's milk, M-D formula	40	9	22.5	21	3	14.3

evaporated cow's milk and maltose-dextrin the mean pH remains at 6.2.

While the over-all incidence of perianal dermatitis varies with the feeding, there are also differences in severity of the disease, and differences in incidence between white and Negro infants. These data are shown in Tables IV and V.

DISCUSSION

Norton and Shohl[4] have listed the mean pH of the stool of breast-fed infants for each of the first ten days of life. Data from this study parallel those findings (Table VI). The difference in level may be attributed to the difference in reference standards between the colorimetric method of Norton and Shohl and the potentiometric method used here.

It has been shown that short-chain saturated fatty acids (C_8 to C_{14}) inhibit the growth of *Lactobacillus acidophilus* and *Lactobacillus bifidus* in the infant's gut,[5, 6, 7] and tend to make a more alkaline stool. The simulated human milk used in the present study differs from the same feedings in the Barbero work only in that it is now made with a reduced proportion of short-chain saturated fatty acids. As anticipated, the mean stool pH of infants fed this product in this study (5.7) is lower than that reported by Barbero and co-workers (6.2) and more nearly approaches that of breast-fed infants (5.4).

The incidence of perianal dermatitis among the infants fed breast milk or evaporated cow's milk and maltose-dextrin follows the same pattern as

TABLE VI. STOOL pH OF BREAST-FED INFANTS FOR THE FIRST TEN DAYS OF LIFE, FROM TWO STUDIES

	pH OF STOOL									
INVESTIGATOR	1ST DAY	2ND DAY	3RD DAY	4TH DAY	5TH DAY	6TH DAY	7TH DAY	8TH DAY	9TH DAY	10TH DAY
Norton and Shohl	6.08	5.98	5.49	5.22	4.90	4.79	4.75	4.87	4.87	4.88
Pratt and Read		6.5	6.3	5.9	5.7	5.4	5.4			

TABLE VII. INCIDENCE AND RACIAL DISTRIBUTION OF PERIANAL DERMATITIS ON TWO FEEDINGS, FROM TWO STUDIES

	PER CENT WITH DERMATITIS					
	WHITE		NEGRO		COMBINED	
FEEDING	PRATT[2]	PRATT AND READ	PRATT[2]	PRATT AND READ	PRATT[2]	PRATT AND READ
Breast milk	7.1	7.7	0	6.7	5.4	7.1
Cow's milk, M-D formula	35.3	22.5	11.0	14.3	33.3	19.7

Comparison of data from this study with data on stool pH published by Barbero and associates[5] shows some coincidence, even though the methods of obtaining specimens and the ages of the babies differ. Barbero and associates report the pH values of stool specimens mixed with water after being obtained by rectal swab from infants 2 weeks to 3 months of age. Their mean for breast-fed babies is 5.5, and for those fed the cow's milk and maltose-dextrin formula 6.7. For infants over 6 days of age in the present study, the respective mean values are 5.4 and 6.2.

that of an earlier study.[2] Comparison is made in Table VII. Although the rates for evaporated cow's milk-fed white infants are not in close accord for the two series of observations, they do serve to illustrate that perianal dermatitis is from three to five times more common in white babies fed an evaporated cow's milk and maltose-dextrin formula than in those who are breast fed.

SUMMARY AND CONCLUSIONS

The pH of the stool, of the perianal skin, and of the axillary skin was measured in 251 infants, predominantly from 2 to 9 days of age. The occurrence of perianal dermatitis was also noted. One hundred forty babies were breast fed, fifty fed a prepared formula approximating breast milk composition and containing only lactose as carbohydrate, and sixty-one fed an evaporated cow's milk and maltose-dextrin formula.

During the first three days of life there was little difference in mean pH observations, regardless of feeding. From the fourth day, pH of the stool and of the perianal skin became increasingly acid for the breast-fed infants and for those fed simulated human milk, but remained relatively unchanged for those fed the cow's milk formula. The axillary skin pH became more acid with age regardless of feeding.

The incidence of perianal dermatitis varied with the pH of the stool and of the perianal skin, being less frequent the more acid the stool and perianal skin.

These findings support the belief that the stool pH of infants is directly affected by the type of feeding. The perianal skin with which the stool comes into contact is correspondingly changed. If the pH of the stool is such that the perianal skin pH is raised above the range found in breast-fed infants, the incidence of perianal dermatitis is increased.

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HYPOPROTEINEMIA AND EDEMA IN ECZEMA

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THERE is very little material in the pediatric literature concerning hypoproteinemia and edema in eczema. It is evident that three factors are involved in the production of hypoproteinemia. It may result from a diet poor in animal protein, from loss of fluids from the skin in weeping lesions, and from infection which interferes with plasma protein synthesis. The combination of all three factors almost always produces hypoproteinemia and edema.

All the cases of atopic eczema that were admitted to the Los Angeles Children's Hospital in the last ten years, where adequate chemical determinations were made, were reviewed. These included twenty-four patients eight of whom had clinical edema. These cases have been summarized in Table I.

The normal blood chemistries for protein according to Nelson[1] are:

Aged 6 months to 1 year, total protein 6.1 ±0.29, albumin 4.97 ± 0.73, globulin 1.38 ± 0.68.

Aged 1 year to 4 years, total protein 6.94 ± 0.47, albumin 4.71 ± 0.12, globulin 2.03 ±0.34.

Twenty of the twenty-four patients with eczema had hypoproteinemia. Eighteen of these showed abnormally low albumin levels and five had low globulin levels.

In reviewing the diets of these children, it was found that the use of a vegetable protein alone, such as soybean milk, favored the development of hypoproteinemia. The presence of adequate amounts of meat in the diet rarely resulted in hypoproteinemia. This is borne out in the reports of nutritional edema in the tropical countries in such a disease as kwashiorkor. In these countries, cow's milk is not available and vegetable proteins are used as a substitute.

Lui and associates[2] reported that vegetable proteins have proved half as valuable as animal proteins in restoring plasma protein. The use of soy increased the incidence of protein deficiency when used as a milk substitute, because of the fact that cysteine is a necessary amino acid in protein synthesis and soy is low in cysteine.

Both human and cow's milk, because of the lactalbumin fraction, are more adequate than soybean milk for protein synthesis. Human milk, because of its greater lactalbumin content, is a little better than cow's milk. Hill[3] suggested that it is desirable to have more than one type of food in order to meet the requirements of growth if the infant is on a milk-free diet. In dogs, adequate food protein has been found to have a qualitative as well as a quantitative significance in the regeneration of plasma protein. The most effective protein was found to be beef serum.[4]

It is, therefore, recommended that all patients with eczema be fed some type of meat early, irrespective of

From the Los Angeles Children's Hospital.

TABLE I

CASE	AGE	TOTAL PROTEIN	ALBUMIN	GLOBULIN	NPN	EDEMA	DIET	WEEPING	INFECTION	DURATION OF ECZEMA IN MO.
1	6 mo.	1.8	1.7	0.1	25	++++	Breast 5 wk. Soybean milk	++++	Urinary tract infection with persistent *B. proteus*	4½
	Poor protein diet and infection. Treated with plasma, intravenous Amigen, human serum albumin, oral Nutramigen, with improvement of edema. ACTH given for 17 days. Total proteins rose to 4.6 and globulin to 1.4. Edema disappeared at total protein level of 4 grams. Cholesterol 78.									
2	6 mo.	1.71	1.64	0.07	31	++++	Soymilk, goat's milk, no meat	+++	No preceding infection Generalized eczema	5
	Very poor diet. No infection. In three weeks on diet of Nutramigen, beef, rice, and banana with no additional therapy, total protein rose to 3.97 grams, and edema disappeared. Cholesterol 90.									
3	8 mo.	1.7	1.0	0.7	29	+++	Soymilk, no eggs or meat	++	Vomiting before admission	3
	Poor meat protein diet and infection. Treated with intravenous Amigen and meat diet. After three weeks total protein rose to 4.1 grams and edema disappeared.									
4	9 mo.	3.8	2.6	1.2	29	++	Soymilk, rice, gelatin, no meat	++	Vomiting and diarrhea	8
	Poor meat protein diet and infection. Improved with intravenous Amigen and Nutramigen orally.									
5	6 mo.	4.0	2.8	1.2		+++	Meat, soymilk, later Nutramigen	++	Upper respiratory infection, T. 104°, infected skin	4
	Adequate meat protein diet, infection preceding edema. Extensive eczema. Gained 3 pounds in one week. Treated with intravenous plasma. Edema improved in one week. Cholesterol 180. Thymol turbidity 4 units, cephalin flocculation negative.									
6	4 mo.	3.0	2.5	0.5	51	0	Goat's milk, cereal	++	T. 106°, convulsion, acidosis, diarrhea, abscess of chest wall, URI, collapse	2½
	Adequate meat protein diet, severe infection with diarrhea. Treated with transfusion, Nutramigen. NPN fell to 30 and total proteins rose to 5.4.									
7	4 mo.	4.1	3.1	1.0		0	Whole milk, soymilk, meat	++++	None	6
	Diet adequate, no infection, no edema, low total proteins due to extensive weeping.									

(Continued on next page.)

TABLE I.—CONT'D

CASE	AGE	TOTAL PROTEIN	ALBUMIN	GLOBULIN	NPN	EDEMA	DIET	WEEPING	INFECTION	DURATION OF ECZEMA IN MO.
8	6 mo.	4.0	2.6	1.4	23	0	Goat's milk, soymilk	+++	Repeated upper respiratory infections with fever	3
		Diet fair, frequent respiratory infections. Given Nutramigen with little change in total protein. ACTH showed little change. Greatest improvement followed cortisone and Nutramigen together.								
9	6 mo.	4.28	2.84	1.44		0	Breast 5 mo. Fruit, goat's milk, soymilk	++++	None	6
		Diet adequate. No infection. No edema. Low total proteins due to fluid loss from extensive weeping lesions.								
10	8 mo.	4.96	3.95	1.01		0	Soymilk, goat's milk, no meat	0	Extensive infected eczema	6
	9 mo.	6.37	3.41	2.96		0	Soymilk, beef, vegetables cereal	0	Otitis media, recurrent extensive eczema	
		Because of adequate meat protein diet, and despite recurrent infection and extensive eczema, total proteins were normal on second admission.								
11	11 mo.	5.46	3.86	1.63	39	0	Nutramigen, meat	++++	Severe generalized eczema	21
		Adequate protein diet, no infection. Despite extensive, recurrent, weeping eczema, no edema or hypoproteinemia was present.								
12	7 mo.	5.59	4.19	1.4		0	Meat and goat's milk	0	None	6½
		Adequate diet, no infection, generalized eczema. Slightly lowered total protein.								
13	4 mo.	5.6	3.7	1.9		0	Similac, cereal	++++	None	2½
		Diet adequate for age. No infection. Severe weeping with slight fall in total proteins.								
14	9 mo.	5.8	4.5	1.3		0	Meat occasionally, whole milk, and vegetables	0	Vomiting two days	6
		Mostly milk diet, mild infection, mild eczema, no edema, normal total proteins.								
15	11 mo.	5.4	3.8	1.6	39	0	Meat, Nutramigen	++	Low-grade infection of skin	9
		Adequate meat protein intake, mild infection, generalized eczema with moderate weeping and slightly lowered total protein.								
16	3 yr.	3.9	2.3	1.6		++	Meat, milk	++++	None	33
		Adequate meat protein diet, no infection, extensive weeping. Edema subsided on high protein diet and transfusions and total protein rose to 5.6 grams.								
17	18 mo.	4.9	3.3	1.6	30	++++	Breast 6 mo., soymilk, no meat	++++	Upper respiratory infection, anorexia	6
		Poor meat protein diet and infection. Given meat formula, intravenous plasma, and Amigen. Edema disappeared and total protein rose to 5.4 grams.								

TABLE I.—CONT'D

CASE	AGE	TOTAL PROTEIN	ALBUMIN	GLOBULIN	NPN	EDEMA	DIET	WEEPING	INFECTION	DURATION OF ECZEMA IN MO.
18	16 mo.	5.0	2.9	2.1	24	++	Goat's milk, soymilk, meat	0	Fever, pharyngitis, extensive exfoliative eczema	15
		Adequate diet, infection preceding edema. Edema subsided with treatment of infection and maintenance of high protein diet.								
19	22 mo.	4.83	3.2	1.71	31	0	Nutramigen, meat	++	Severe generalized eczema	21
		Adequate protein diet, no infection. Generalized eczema with weeping and low total protein.								
20	18 mo.	5.9	4.2	1.7	30	0	Meat, milk	+	None	12
		Adequate meat protein diet. No infection. Generalized eczema with mild weeping. Normal total protein.								
21	23 mo.	5.9	4.1	1.8	36	0	Goat's milk, beef, rice, vegetables	0	None	22
		Adequate meat protein diet, no infection. Moderate eczema. Normal total protein.								
22	2½ yr.	6.0	4.0	2.0	33	0	Meat, poor milk intake	++	None	22
		Adequate protein diet, no infection. Extensive exfoliative eczema with mild weeping. Normal proteins.								
23	5½ yr.	6.6	3.9	2.7		0	Meat, milk	0	None	60
		Adequate diet, no infection, recurrent extensive eczema on three admissions. Normal proteins.								
24	15 mo.	6.9	4.8	2.1	32	0	Cow's milk exclusively, 50 ounces daily	0	T. 101°, upper respiratory infection, urinary tract infection	5
		Mostly milk diet, infection, nutritional anemia. Mild eczema, normal total protein.								

what type of milk or milk substitute is used. This is contrary to the concept of Finkelstein,[5] who felt that the presence of animal protein increased the itching or, as he called it, the angioneurotic pruriginous component of eczema. He recommended that the diet should consist primarily of fruit, vegetables, and vegetable protein.

As recommended by Hill,[3] it was also found that the use of amino acids, such as Nutramigen, was a good source of nitrogen for protein synthesis.

Beling and Lee[6] report a case of eczema, edema, and hypoproteinemia in an 8-month-old child, where the feeding of protein hydrolysate produced a rise in the total proteins and disappearance of the edema.

However, poor diet alone, without excessive weeping or infection, rarely produced marked hypoproteinemia. Similarly, where the eczema was extensive, but weeping was nonexistent, and the meat protein diet adequate, the total protein usually showed no significant changes in the cases reported.

Evidence speaks in favor of the liver as the major site of albumin production and much of the globulin.

Madden and Whipple[7] state that the plasma protein-forming mechanism is disturbed by infection. There is experimental evidence that infection can limit production of plasma protein in plasma-depleted dogs.

The history of an infection antedating the appearance of edema evidently was the trigger mechanism in its production in five of the seven cases that developed edema. Infection probably produces a temporary disturbance of the liver function, causing a deficiency in the synthesis of protein. However, the giving of a high protein diet and intravenous Amigen or plasma rapidly produced an increase in total proteins usually within one to three weeks, showing that this failure in liver protein synthesis is a transient disturbance. In two of the patients with edema, where liver function tests were done, the total cholesterol was low, 78 and 90 mg. per 100 c.c.

Jonsson and Lagercrantz[8] report a case of edema and hypoproteinemia in a 19-month-old child, with normal liver function tests, where autopsy revealed interstitial fibrosis of the liver. They question whether the liver damage is primary or secondary, but emphasize the findings of normal liver function tests in the presence of a damaged liver.

It is evident that one may get normal liver function tests where edema and hypoproteinemia are found, even in the presence of liver damage, and that transient liver damage may be the etiological factor in the production of hypoproteinemia.

In contrast, it is interesting to note that in eighty-five cases of varying types of chronic dermatoses and eczema where no infection was present, Ayres and associates[9] reported diminished liver function as demonstrated by the bromsulfalein excretion test.

DISCUSSION

Wolpe,[10] in 1947, described the nutritive crisis seen occasionally in infants suffering from universal eczema or erythroderma. The typical course is a rapid loss or gain of weight, associated with apathy, refusal of food, and diarrhea. Investigation revealed blood protein deficiencies, which were the more difficult to restore to normal depending upon the length of time that the deficiency existed.

Wolpe,[11] in a subsequent article, reviewed the blood protein findings in fifty-four cases and found that 26 per cent showed a protein deficiency. He divided hypoproteinemia into three types. The prehepatic type was due to interference with the intake, digestion, or absorption of proteins. The hepatic type was due to the inability of the liver to synthesize protein despite adequate supply of protein-building material. The posthepatic type was due to an abnormal loss of protein despite an adequate supply and synthesis.

It is evident that all three types are present in eczema. The prehepatic type is due to poor diet, the hepatic type can follow either skin or parenteral infection, and the posthepatic type can be due to protein serum loss from a weeping skin.

Wolpe,[11] reported the tendency for the globulin fraction to show a greater deficiency than the albumin fraction in his hypoproteinemic children with eczema. Cooke and coworkers[12] found that the significant

drop in eczematous children was primarily in the albumin fraction. Kagan[13] studied 345 patients with hypoproteinemia and found the decrease due almost invariably to a decrease in albumin. This is in accord with the knowledge that the osmotic influence of albumin in maintaining blood volume is four times greater than the globulin. In our studies the maximum drop is in the albumin fraction, occurring in eighteen cases, and a low globulin fraction was present in five cases. It should also be noted that in infants under one year, a much greater drop in protein was necessary to produce edema than in the children over one year of age.

Several cases of hypoproteinemia and edema have been reported recently in children. Such reported cases of low albumin, low globulin, and low gamma globulin fractions fall into two clinical types. The first type due to a defective congenital formation of albumin, globulin, and particularly gamma globulin is described by Schick and Greenbaum.[14] This child had bouts of edema from the age of 12 weeks. Despite the low albumin, low globulin, and almost complete absence of gamma globulin by electrophoretic analysis, the child was rarely ill. A high protein diet, amino acids orally, and antigenic stimulation did not affect the level of serum proteins, nor the clinical picture of recurrent edema. These authors postulate a congenital deficiency in the liver, bone marrow, or reticuloendothelial system which accounts for the inability to properly synthesize plasma protein. They felt, however, that the most probable site is in the liver. The liver function test in this case revealed a normal cholesterol, cephalin flocculation test, but a mildly elevated hippuric acid test.

Another case reported by Thompson and associates[15] revealed idiopathic edema and hypoproteinemia since the age of 13 months. Diet did not affect the protein level. The patient manifested an unmistakable deficiency in the mechanism of fabricating serum proteins. Liver function tests were not significant. This patient finally succumbed to infection at the age of 3½ months. Autopsy revealed primary atrophy of the hepatic cords, but no evidence of fibrosis or inflammatory changes in the liver. The authors assumed a congenital anomaly in the function of the liver due to a reduced amount of liver tissue.

Other cases of idiopathic hypoproteinemia and edema on a congenital basis have been reported in the literature in adults.[16, 17, 18]

The second type of hypoproteinemia and edema reported is due to disturbance of the plasma-forming mechanism by infection.

Jonsson and Lagercrantz[8] report a case of hypoproteinemia and edema in a 19-month-old infant. Liver function tests were normal, but, on autopsy, interstitial fibrosis of the liver was found. They refer to three other cases in children reported by Odegard[19] and Jones,[20] where hypoproteinemia and edema were found associated with cystic fibrosis of the pancreas. Autopsy in these cases revealed fatty degeneration of the liver and fibrosis of the pancreas. Jonsson and Lagercrantz conclude

that there is a connection between hypoproteinemia and hepatic damage, even though no disturbance of liver function may be demonstrated clinically or on the basis of laboratory data.

Those cases reported as congenital hypoproteinemia and edema were irreversible, despite adequate high protein diets. However, those cases secondary to dietary deficiencies or infections usually are reversible.

A case similar to those reported in this review is described by Fried and Henley.[21] They report a case of deficiency in gamma globulin in a 10-week-old child with edema and hypoproteinemia. The studies were done by protein fractionation. It is interesting that this infant was an allergic child with a skin eruption and was almost exclusively on a soybean formula. The cholesterol was low, the cephalin flocculation was 3 plus, and the thymol turbidity was 1.4 units. When the formula was changed to Nutramigen, the edema disappeared within a week, and the total protein as well as the gamma globulin fraction increased.

TREATMENT

In all eight cases of edema, the edema was reversible, usually improving within one to three weeks. Treatment consisted of a diet high in meat protein, or Amigen or Nutramigen. Intravenously, whole blood, Amigen, or plasma was given. The skin, if weeping, was treated with wet compresses and subsequently followed with the customary ointments used in eczema. Infections were treated with the necessary antibiotics, usually penicillin and streptomycin.

The value of ACTH and cortisone in states of hypoproteinemia and edema in eczema could not be definitely evaluated. The steroids were used in two cases and produced an increase in the total proteins.

SUMMARY

1. Twenty out of twenty-four cases of eczema that were reviewed had evidence of hypoproteinemia.

2. Eight of these cases had clinical evidence of edema.

3. The factors predisposing to edema were extensive weeping of the skin, a diet poor in animal protein, and infection.

4. In an extensive eczema, particularly where soybean milk is used exclusively, meat should be introduced at an early age.

5. Treatment consisted either of amino acid feedings, high animal protein diet, and Amigen, plasma, or blood intravenously.

6. Eighteen of the cases showed abnormally low albumin levels and five low globulin levels.

7. It is postulated that infection which triggered the appearance of edema may produce transient liver damage and hypoproteinemia without concomitant abnormal liver function tests.

8. A much lower serum protein was necessary to produce edema in children under one year than in those over one year.

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On Triplets

We hear from Medway, that on the 11th Instant, the Wife of Mr. Job Plimpton of that Place, was brought to Bed of three living Children, all Girls, but are since Dead. And her Sister (from whom we have this Account) doubts not, but that with as active an Husband she might do the same, And, From Ipswich, That the Week fore last, A Woman of that Place was bro't to Bed of three Children, two of which are since dead, the other is like to live.

BOSTON GAZETTE OR COUNTRY JOURNAL, AUGUST 4, 1755.

ACUTE INTERMITTENT PORPHYRIA

Report of a Case in an Infant Aged Eight Months, With Discussion of Porphyrin Metabolism

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THE porphyrins are a class of pigments of wide distribution in animal and plant tissues. They occur in many common foods such as potatoes, bread, milk, fish, and spinach. They make up an essential part of the respiratory pigments and enzymes—hemoglobin, myoglobin, catalase, peroxidase, and chlorophyll. Their occurrence in the latter compound explains the universality of their distribution in leaves and grasses. Porphyrins are found in the young red cells of human bone marrow, but none have been demonstrated past the normoblast stage. The porphyrins are red in organic solutions, red-purple in mineral acid solutions, and red-brown in alkaline solutions.[48] Under the Wood lamp they have a brilliant red fluorescence.[51]

STRUCTURE OF THE PORPHYRINS (FIG. 1.)

Chemically, the porphyrins are rather stable compounds consisting of four pyrrole nuclei connected in a ring by methene bridges to form the "porphin" nucleus common to all porphyrins.

The origin of the body's supply of pyrroles for such formation is unknown. However, chemically, porphyrins can be synthesized from simple organic compounds such as aminoacetic acid and formyl acetone, and in vivo they are manufactured by the ordinary yeast cell. The porphyrins, both known and surmised, can be formed by substitution of various groups of radicals on the basic "porphin" ring, and by different sequential arrangements of the same groups.

Hans Fischer was the first to demonstrate that if the "porphin" ring were considered to have methyl and ethyl groups substituted on it as side chains, four isomeric combinations were possible. These were called, for classificatory purposes, the etioporphyrins. They are chemical compounds only and do not occur in nature.

Only types I and III coproporphyrins or uroporphyrins occur naturally or are associated with human disease, and neither type may be derived from the other. Thus it is felt that the coexistence of types I and III porphyrins in the same individual must represent an independent synthesis of each type. This is, in brief, Fischer's theory of the "dualism" of the porphyrins.[12]

Simple conversion of the ethyl radicals of etioporphyrins I and III to propionyl groups gives, respectively, coproporphyrins I and III. The coproporphyrins are so named because they were first isolated from human feces; they occur normally in small amounts in human urine and feces,

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and in increased amounts in various disease conditions which will be discussed later.

One more chemical step, the conversion of the methyl groups of coproporphyrins by carboxylation to acetic groups, creates uroporphyrins. Whether this is the biologic mechanism of uroporphyrin formation in disease processes associated with excretion of uroporphyrins or whether they are independently synthesized without having to go through a coproporphyrin "stage" is unknown.

At this point, it should be emphasized that the formation, storage, or excretion of uro- or uro-type porphyrins in measurable amounts is never physiologic and in the human being is always associated with the group of inborn metabolic errors known as the porphyrias.

It can be seen that protoporphyrin (the pigment of hemoglobin) is a

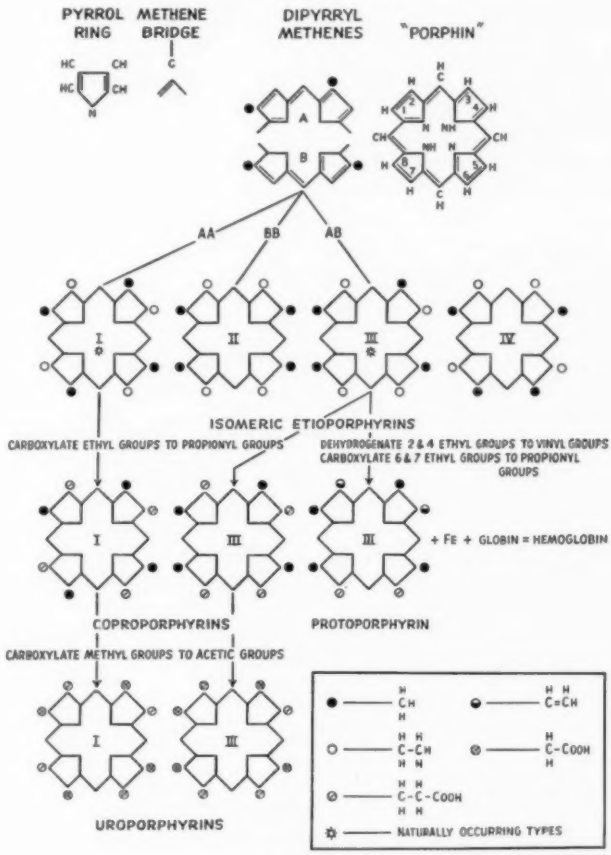

Fig. 1.

type III etioporphyrin isomer in which two ethyl groups have been carboxylated to form propionyl groups and the two other ethyl groups dehydrogenated to vinyl radicals.

In the synthesis of blood pigment, glycine and acetate supply nitrogen and carbon atoms for the formation of dipyrryl methenes which are then condensed to form porphyrins.[29] Protoporphyrin III later combines with iron to form the prosthetic group of hemoglobin. A minute amount of type I isomer is also normally synthesized and excreted by this process in the ratio of about 10,000 parts type III (protoporphyrin) to 1 part of type I (coproporphyrin). Dobriner and Rhoads[9] have suggested that if any two substituted dipyrryl methenes (denominated A and B) are joined to form porphyrins, there may theoretically be three combinations—AA, AB, or BB; the proportions of the compounds so formed are thought to be governed by an enzyme system.[27] Thus both types I and III are formed by the same reaction, yet neither type may transpose to the other. This is probably the best explanation of Fischer's theory of "dualism" and also explains why it is possible to form so much of type III isomer (protoporphyrin for hemoglobin) with so little of type I (coproporphyrin).

IDENTIFICATION OF PORPHYRINS

The various types and compounds of porphyrins may be identified by their solubilities, pH fluorescence curves, absorption spectra, and the melting points of their methyl and ethyl esters. Paper chromatography has been found useful[34] in the identification of the naturally occurring porphyrins.

PHYSIOLOGY AND METABOLISM OF THE PORPHYRINS

While any discussion of the physiology and metabolism of the porphyrins and their diverse facets as exhibited in the human organism would be completely outside the scope or the interest of most pediatricians, some brief statement of known facts may clarify the subject. For more extensive reviews, the reader is referred to Watson and Larson,[45] Waldenstrom,[36] Mason and associates,[19] Watson,[48] and Dobriner and Rhoads.[9]

It has been shown that ingested porphyrins are not absorbed from the human gastrointestinal tract. Watson and Larson[45] proved that feeding coproporphyrins I and III to normal individuals does not cause increased coproporphyrinuria and that practically all such ingested coproporphyrins are recovered in the feces. Therefore, it must be considered that any coproporphyrin excreted in the urine or feces is largely endogenous in origin. Dobriner and Rhoads[9] have stated that injected porphyrins do not traverse the placenta, yet normal meconium is found to contain coproporphyrin I, apparently synthesized by the embryo.[9, 33] One interesting report[49] describes a case of "passive porphyrinuria" in an infant born to a mother who was in an acute attack of porphyria. The child excreted decreasingly excessive amounts of coproporphyrin and uroporphyrin during the first year of life, after which excretions of these substances gradually fell to normal. This would seem to indicate that the placenta

may be permeable to excessive amounts of normally occurring porphyrins or to abnormal porphyrins.

In normal individuals, Watson[48] found the urinary excretion of coproporphyrins to be roughly between 60 and 300 μg per day, approximately 80 per cent of this as coproporphyrin I and 20 per cent as coproporphyrin III. The total excretion, urinary and fecal, was found by Brugsch[2] to be 200 to 400 μg daily, although others feel that excretions up to 1,000 μg daily are normal. Protoporphyrin occurs in normal feces, partly exogenous as a result of bacterial action on dietary hemoglobin in the presence of protein,[35, 42] and partly endogenous from bile. This endogenous fraction may be derived from the protoporphyrin of red cells or from the immature cells of the marrow.[30]

TABLE I

	CONGENITAL	ACUTE INTERMITTENT	CHRONIC OR CUTANEA TARDA	NORMAL
Age at onset	Infancy or childhood	Young adulthood	Late adulthood	
Genetics	Mendelian recessive	Mendelian dominant (not sex-linked)		
Sex predilection	More often in males 4:1	More often in females 3:1		
Color of urine	Burgundy red	May be normal (darkens on standing)	Red or dark	
Clinical findings	Erythrodontia Severe photosensitivity (hydroa aestivale) Hirsuitism or other evidence of endocrine imbalance	Cramping abdominal pain Paresis or ascending flaccid paralysis Psychic disturbances	Mild photosensitivity Mild abdominal pain Skin pigmentation	
Chemical findings				
Porphobilinogen in urine	Absent	Present	Absent	Absent
Uroporphyrin in urine	Predominantly type I	Predominantly type III	Types I and III	Absent
Urinary coproporphyrins	Increased: predominantly type I	Increased: predominantly type III	Increased: types I and III	Circa 60-300 μ (80% type I)
Zinc porphyrin	Absent	Present	Absent	Absent
Marrow porphyrin	Markedly increased	Normal	Normal	Normal

SPECIFIC DISEASES OF PORPHYRIN METABOLISM

Porphyria is defined as a rare inborn metabolic error in which the basic fault is formation, storage, and excretion of uroporphyrins. It should be understood that the term "porphyrinuria" implies excretion of excess porphyrins as a result of a disease which is not necessarily related to any inborn metabolic error. Some of the disease processes causing porphyrinuria will be discussed later. The outstanding characteristics of the known types of porphyria as contrasted with the normal are shown in Table I.

Typically, acute intermittent porphyria is a chronic metabolic disorder, inherited as a mendelian dominant, characterized by acute exacerbations alternating with remission periods of varying duration. In an acute attack, cramping adbominal pain, obstinate constipation, ileus, nausea and vomiting, jaundice, leukocytosis, and fever may be seen in association. Neurological symptoms and signs may include paresthesias, pareses, amblyopia, paralyses, convulsions, and muscular atrophy. Psychic symptoms such as hallucinations, delirium, mania, and psychoses may occur. Symptoms referable to the cardiovascular system include hypertension, tachycardia, and oliguria. It is important to remember that symptoms attributable to various bodily systems may occur singly or in combinations.

The urine in acute intermittent porphyria may be normal in color and only darken to the characteristic port-wine color on standing. The change in color is accentuated and accelerated by direct sunlight. The Watson-Schwartz test[44] for the presence of porphobilinogen (a colorless chromogen precursor of the porphyrins) is highly specific and is considered pathognomonic of the disease.[39] In a series of 1,000 such tests done consecutively, no false positives were encountered.[15]

Usually, acute porphyrias have been divided into idiopathic and toxic, the basis for separation being merely identification of a causative agent in the latter. "Toxic" cases would be better classified as porphyrinurias since no hereditary metabolic error is thus connoted without some tissue insult from a chemical agent. Both Turner[33] and Nesbitt[24] have shown the familial nature of true acute intermittent porphyria. This is an important point because acute attacks have been precipitated in supposedly healthy members of porphyriac families by large doses of barbiturates.[36]

Death in acute intermittent porphyria most often is due to respiratory center involvement from ascending flaccid paralysis. This palsy may, however, be transient and reversible. The cerebrospinal fluid usually shows no abnormalities, although increase in protein and cells has been observed, and porphyrins have been demonstrated in the cerebrospinal fluid.[17, 26, 50]

The mortality in the acute attack of intermittent porphyria associated with paralysis has been variously estimated at from 50 to 80 per cent.[19] In more recent communications, Nesbitt[24] and Nesbitt and Watkins[22] have suggested that the disease may be much more prevalent than reported cases would indicate and that therefore its prognosis may not be as gloomy as previously had been estimated. It must be remembered that survival of one acute episode does not dispose of the underlying fault in the patient's porphyrin metabolism.

The occurrence of the acute intermittent type of porphyria in childhood is most unusual and onset of such a severe attack in the age group of the patient to be reported is unknown in so far as can be determined from an exhaustive survey of the literature. Rothman[28] described acute porphyria in a Negro boy 3 years 8 months of age, apparently the youngest proved case.

CASE REPORT

B. T., 8-month-old first-born female child of healthy Caucasian parents, was admitted to Wesley Hospital on Oct. 5, 1953, with the following history: She was the product of a normal pregnancy and delivery. Developmental pattern was normal; she had sat alone at 5 months, had pulled up to furniture and walked about her crib at 8 months. She had been fed adequately and had been given supplemental vitamins from the age of one month. There was no history of heredofamilial disease of any type. She had never had any illnesses nor had any drugs ever been administered. There was no exposure to lead or any other toxic substance.

On Oct. 4, 1953, the mother had thought that the child seemed undesirous of standing and did not move her legs as much as usual, but since the child seemed in no distress and had no fever, she was put to bed after eating a good evening meal. Four hours later she had begun to cry out in her sleep and continued to moan throughout the night. The next day she was unable to stand or to move the lower extremities voluntarily and was referred for diagnosis. At no time had there been any fever, convulsions, tremors, or vomiting, and bowel and bladder functions were normal even after paralysis supervened.

Upon admission, the child's temperature was 97° F. rectally, the pulse was 140, and respirations were 28. She was obviously a bright, well-developed and well-nourished child. She was in no acute distress, although crying from time to time for short intervals during the examination. There was no hirsutism, the head was of normal size and shape, and the external ocular movements were normal, except for an esophoria of the left eye, which both parents and the referring physician stated to have been present since birth. The fundi were normal; the four central incisors were already erupted; no erythrodontia was observed nor was there any fluorescence of the teeth when examined later by Wood lamp. The abdomen did not seem tender. The baby voided clear urine and had a normal bowel movement during the examination. The pertinent findings were mainly neuromuscular. In the lower extremities, there was loss of knee and ankle jerks with only faint withdrawal to painful or hot stimuli and obvious severe loss of motor power. Abdominal reflexes were present. All tendon reflexes and muscular power in the upper extremities were normal.

The admission blood count was 11,950 white blood cells with 48 per cent polymorphonuclears, 11 per cent nonfilamented forms, 45 per cent lymphocytes, 6 per cent monocytes, and 1 per cent eosinophils. The red blood count was 4.1 million with 11.5 grams of hemoglobin. Examination of the spinal fluid showed a cell count of 3 lymphocytes per cubic millimeter, a total protein of 19 mg. per cent, and a sugar of 50 mg. per cent. Culture of the cerebrospinal fluid revealed no organisms. Routine urinalysis was negative with an acid reaction. The serum potassium level was 5.07 meq. per liter.

The next morning, a test for porphobilinogen was requested. This was strongly positive, and a reddish fluorescence was obtained on transillumination of the urine with the Wood lamp. Repeated tests for porphobilinogen by the method of Watson and Schwartz[44] were positive. The urine became dark red after exposure to sunlight in open air for eight hours or more. X-ray examinations of the skull and chest were negative; the long bones showed no evidence of vitamin deficiency or heavy metal deposition. A repeat examination of the cerebrospinal fluid on Oct. 8, 1953, showed no cells, a protein of 50 mg. per cent, and a negative test for porphyrins in the cerebrospinal fluid.

The cephalin flocculation test was negative at twenty-four and forty-

eight hours on that date; the thymol turbidity was 1.39 units; the total serum protein was 6.5 grams per 100 c.c. with albumin making up 4.1 grams per 100 c.c. of this.

The child's course in the hospital was one of gradual improvement; she ate and slept well and gained weight normally. Never was there any elevation of temperature. The porphobilinogen reaction became less strong in the urine as her recovery of power in the lower extremities progressed. She was discharged on the sixth hospital day, and at this time showed some faint return of deep reflexes. Over the next month, she regained full use of her lower extremities with return of all deep reflexes, and at 9 months had learned to walk unsupported. The Watson-Schwartz test was still faintly positive and the cerebrospinal fluid examination was completely normal at this time. Examinations of the urines of both parents were negative for porphobilinogen.

PHYSIOLOGIC AND PATHOLOGIC CONDITIONS WITHOUT METABOLIC DEFECT WHICH ALTER PORPHYRIN EXCRETION

As previously mentioned, Watson[40] has demonstrated a range of coproporphyrin excretion in the urine of normal individuals of from 60 to 300 μg per day. The isomer distribution, as reported by the same author[41] was from 48 to 92 per cent of type I and from 8 to 52 per cent of type III. Watson feels the normal fecal excretion of coproporphyrin is in the range of 150 to 400 μg daily.

Since protoporphyrin is necessary for hemoglobin synthesis and since it has been shown that only the young red cells contain free porphyrins, it might be assumed that conditions associated with erythropoiesis and attempts at hematopoietic activity on the part of the bone marrow would associatively cause increased excretion of urinary and fecal type I coproporphyrins since they are probably the result of hemoglobin breakdown. This is true in the main and is seen in hemolytic jaundice,[42] hemorrhage,[6] sickle-cell disease, and pernicious anemia as it first responds to therapy.[5] In almost any condition in which the marrow is trying to elaborate an increased number of cells, fecal and urinary coproporphyrin excretions are increased. Conversely, decrease in coproporphyrin I excretion and increase in coproporphyrin III output occurs in conditions associated with a hypoplastic bone marrow. This is thought by Watson[48] to be related to abnormal synthesis of hemoglobin due to toxic or chemical factors. Since the fecal porphyrin is considered to enter the intestinal tract through the biliary system, it might be expected that many types of liver derangement would influence porphyrin excretion, with variation in the ratio of porphyrin types excreted in feces and urine. This is true in cirrhosis, acute infectious hepatitis, toxic hepatitis, subacute yellow atrophy, and mechanical jaundice due to malignancy or gallstones.[23] In all these, the increase is in coproporphyrin I, although, oddly enough, most cases of alcoholic cirrhosis and malnutrition show increased type III coproporphyrin excretions in the urine.[45]

Many febrile conditions and infectious diseases seem to produce increased type I coproporphyrinuria.[4] Whether this is due to the usual cloudy swelling of the liver in such ailments or to some more obscure mechanism is unknown.

An interesting fact is that the viruses of infectious hepatitis and of poliomyelitis whose preferential organs of attack in the body are so diverse, both cause increased urinary coproporphyrin excretion. In the former, the major increase is in type I; in the latter, type III.[46]

Increased urinary excretion of type III coproporphyrin is seen in poisoning with the heavy metals, lead being the metal which gives the highest urinary values for coproporphyrin.[41]

Other drugs have been blamed for cases of acute "toxic" porphyrinuria. Chief among these have been Veronal (barbital, U.S.P.), Trional (sulfonethylmethane, N.F.), and Sulfonal (sulfonmethane, N.F.), although various other hypnotics and sedatives have been incriminated, as have sulfonamide compounds. Waldenstrom's[37] report would indicate that many cases of "toxic" porphyria only represent a "lighting-up" of a process previously present, though latent. So far as is known, no symptoms in any of the disease processes just mentioned are referable to the increased excretion of porphyrins.

PHYSIOPATHOLOGIC EFFECTS OF THE PORPHYRINS

The relationship of known porphyrin effects to the clinical symptoms produced by acute porphyria is not completely correlative, since it is well known that though symptoms may abate, the excretion of porphyrins may or may not continue at the same rate. Pain, nausea and vomiting, and obstipation are felt to be caused by the action of porphyrins on either the smooth muscle of the intestinal tract or the abdominal sympathetic ganglia.[19] This, in turn, explains the ileus usually present, with alternating areas of spasm and atony in the bowel. It has been suggested that the symptoms of paralyses and pareses are due to toxic action of porphyrins on the nervous system. Thorner[32] has shown that severe multiple neuritis has occurred during hematoporphyrin therapy and has assumed that this allegates a toxic effect of the porphyrins on the peripheral nerves. The psychic manifestations of delirium, hallucinations, and mania are unexplained. No definite proof of increase in uro- or coproporphyrin in the nervous systems of individuals dying of central nervous system involvement in an attack of acute porphyria has been reported.

All of the cardiovascular symptoms have been ascribed to angiospasm. Hypertension, spasm of retinal arteries, tachycardia, and electrocardiographic changes suggesting transient ischemia have been observed.[10]

Pigmentation and light sensitivity are thought due to the photodynamic action of the porphyrins.[31]

PATHOLOGIC FINDINGS

The correlation of the clinical findings in the acute disease with necropsy reports is again disappointing. In the central nervous system, there have been found various microscopic changes indicative of neuronal degeneration. Demyelinization and degeneration of the peripheral nerves are common. Pigment deposits, both iron containing and noniron containing, are found throughout the central nervous system and the cells of the sympathetic ganglia.[1, 2, 19]

The parenchymal and reticulo-endothelial cells of the liver may show cloudy swelling with intracellular de-

posits of pigment. There is excess porphyrin in the liver and a decrease in hepatic catalase. The spleen and kidney show mild generalized degenerative changes and pigment deposits. Both voluntary and cardiac muscle fibers show atrophy and degeneration.

DIFFERENTIAL DIAGNOSIS OF ACUTE PORPHYRIA

In any disease complex with such protean manifestations, diagnosis is only possible by associative thinking in any unexplained case of either acute abdominal pain or sudden paralysis.

Many patients in whom abdominal complaints predominate have mistakenly been thought to have acute intra-abdominal disease demanding surgery. However, despite pain, tenderness, ileus, fever, and leukocytosis, characteristically, the abdomen is soft and rebound tenderness is not elicited. This should put the examiner on his guard.

Any acute disease process capable of causing sudden paralysis may be confused with acute porphyria in which symptoms referable to the central nervous system predominate. Acute infectious polyneuronitis, poliomyelitis, encephalitis, intracranial space-occupying lesions, tick paralysis, diphtheria, hysteria, muscular dystrophies, multiple sclerosis, serum paralysis, cerebral vascular accidents, periarteritis nodosa, acute nephritis, and poisonings must be considered.[24]

The cardiovascular findings may cause confusion with myocardial disease, hypertension from any cause, Addison's disease, acute rheumatic fever, and acute nephritis.

Diagnosis hinges ultimately on the demonstration of abnormal fecal or urinary porphyrins and/or the excretion of excessive amounts of normally occurring porphyrins, and/or the demonstration of porphobilinogen in the urine.

TREATMENT

There is no specific therapy in acute porphyria. If any drug is suspected as a precipitating factor, it should, of course, be withdrawn. Otherwise only supportive and symptomatic measures are of use; attention to diet and good nursing care are essential in an acute phase. If ascending paralysis occurs, a respirator may be lifesaving, and, if bulbar paralysis develops, tracheotomy should be performed as well. The prevention of contractures and decubiti is of vital importance in that many of these patients, after the acute attack has passed, regain a surprising degree of neuromuscular function. Recovery may be hastened by judicious physiotherapy. While it has been shown that liver extract given intramuscularly decreases excretion of coproporphyrins, it is doubtful that this influences the course of the disease.[8]

The use of riboflavin, thiamine, folic acid, and vitamin B_{12} in the treatment of acute porphyria has proved valueless. Watson[48] states that "if there is any evidence of heightened blood destruction or increased erythropoiesis, especially if associated with splenic enlargement, splenectomy is believed to be indicated."

Treatment with ACTH and cortisone seems to offer little in the disease,[13, 21, 23] although favorable re-

sults are reported.[16] In the rare case of acute porphyria where photosensitivity is found, shielding of the eyes and the skin from direct sunlight should, of course, be carried out.

SUMMARY

A case of acute intermittent porphyria in an infant is reported. A brief discussion of the chemistry of the porphyrins and their relationships to human disease is appended.

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PRESACRAL RETROPERITONEAL GANGLIONEUROMA IN A 4½-YEAR-OLD CHILD

Report of a Case and Review of the Literature

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IN VIEW of the relative rarity of occurrence of benign ganglioneuromas in the lumbosacral area in infancy and childhood, the lack of clinical consideration of this neoplasm in the differential diagnosis of abdominal and pelvic masses, and the obvious congenital origin of these neoplasms, it is felt that attention should be focused on lumbar and sacral benign ganglioneuromas by both pediatrician and surgeon alike.

CASE REPORT

B. S., a 4½-year-old white female child, was admitted to Children's Hospital, Washington, D. C. (Case Record No. 51-13973) on Oct. 4, 1953. This child was seen several days before admission to the hospital in an acute episode of viral gastroenteritis. On examination of the abdomen at that time, a mass was discovered. Hospitalization was effected after the intestinal symptoms had subsided. This child was operated on at Children's Hospital, Washington, D. C., on Nov. 28, 1951, for acute suppurative appendicitis. Removal of the appendix was uncomplicated. There was no mention in the operative note of any abdominal or pelvic mass. Convalescence was uneventful. The past history otherwise includes only the usual childhood diseases and routine immunizations. Family history was noncontributory. The mother, father, and two younger female siblings are alive and well. Physical examination revealed an alert, cooperative white female child who was completely asymptomatic. Rectal temperature was 98.6° F. The positive findings were limited to the abdomen where there was a large, firm, nontender, fixed mass the size of a "very large tomato," centrally located between the umbilicus and pubis. Rectal examination revealed the same mass, centrally located and very firm to the palpating finger. Urinalysis was negative. Routine blood work was as follows: hemoglobin 12.4 gram, micro-hematocrit 39 per cent, white blood count 4,500, polymorphonuclears 35 per cent, lymphocytes 62 per cent, and monocytes 3 per cent. Gastrointestinal series and barium enema: There was a midline mass in the pelvis measuring 9 by 11 cm. displacing the small intestine superiorly. Both the rectum and the sigmoid appeared to be compressed and displaced by the mass, the sigmoid being displaced to the right and anteriorly. Intravenous pyelogram: Ureters were normal in caliber. The lower portion of the right ureter was not visualized at any time. The lower portion of the left ureter was displaced laterally by the mass.

On Oct. 9, 1953, laparotomy was performed by Dr. Luther W. Gray under nitrous oxide-ether-oxygen anesthesia. The abdomen was opened in a routine manner, and a large retroperitoneal mass was felt displacing the abdominal organs upward. The peritoneum was incised over the mass which was felt to be encapsulated. When adhesions had been freed by blunt dissection, it was discovered that the mass emanated from a stalk which contained blood vessels and was attached in the hollow of the sacrum. The mass was dissected free, the stalk divided between clamps, and all bleeding controlled. The abdomen was

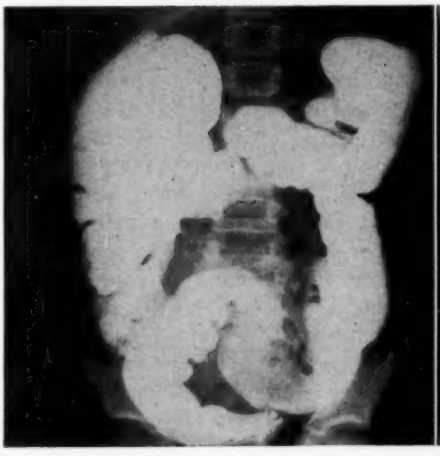

Fig. 1.

Fig. 2.

Fig. 1.—Barium enema before evacuation, showing rectum and sigmoid displaced upward and anteriorly.

Fig. 2.—Five-hour plate—gastrointestinal series showing upward displacement of small intestine.

Fig. 3.—Ten-minute plate—intravenous pyelogram showing centrally located tumor mass with displacement of left ureter.

closed in a routine manner without drainage. The specimen was a firm tumor mass weighing 265 grams and measured 12 by 8.5 by 5.5 cm. On section it appeared glistening and gelatinous. Microscopic diagnosis: Ganglioneuroma. On the fourth postoperative day the child complained of some pain in the left posterior thigh, knee, calf, and dorsum of the foot which was aggravated by extending the knee or by pressure over the course of the left sciatic nerve. Reflexes were normal. However, weight-bearing on the left lower extremity was very painful and was accompanied by a marked limp. This pain subsided somewhat, and after an otherwise uneventful postoperative course, the child was discharged on the seventh day after operation. At home, gradually increasing periods of weight-bearing and exercise, in combination with heat, massage, and vitamin B complex in large doses, were employed. The limp completely disappeared within eight weeks after operation. However, for eight months after operation there was slight tenderness along the course of the sciatic nerve, making sitting in a chair with even weight distribution difficult. At the last examination on June 17, 1954, this child was in excellent health without evidence of recurrent tumor growth or sciatic pain.

DISCUSSION

Benign ganglioneuromas have been reported in the knee, eyelid, scalp, subcutaneous tissues, uterus, ovary, cervix, suprarenal glands, pelvis, appendix, mesentery, thorax, neck, ganglions, nerve roots, cranial nerves, central nervous system, and sympathetic nervous system. The very first description of a ganglioneuroma was reported by Loretz[1] in 1870. The first occurrence in the lumbosacral retroperitoneal area was described by Chiari[2] in 1898 and again reported by Cripps and Williamson[3] in 1899. However, if sixteen years is marked the age limit of childhood, there have been only twenty-eight reported cases, including this one, since 1870 occurring during infancy and childhood in the lumbosacral retroperitoneal area. The age incidence has varied from 19 months to 16 years. Eleven cases (39.3 per cent) have occurred in the 3- and 4-year age group. Fifteen cases (53.6 per cent) have occurred in the 3- through 6-year age group. Eleven (39.0 per cent) of the twenty-eight cases were reported male and seventeen (61.0 per cent) female. The location of the tumor mass was described in seventeen cases (61 per cent) as lumbar, in three lumbosacral, in two presacral, in one precoccygeal, in three pelvic, and in two paravertebral. In one case the tumor was a chance autopsy finding. The other twenty-seven cases were explored surgically. In twenty-two (81.5 per cent) of these cases complete removal of the tumor mass was effected. Two were considered inoperable and biopsied only. One of these patients[4] was alive and well twenty-five months after operation, without apparent increase in size of the palpable abdominal mass; the other died of concurrent miliary tuberculosis.[5] In Jackson and Babcock's[6] case the tumor was removed piecemeal. Total removal, however, was impossible because of the very dense adhesions surrounding the abdominal aorta. In Neumann's[7] case, where the tumor mass was present in both broad ligaments, the right side was operable but the left considered not. In many instances dense adhesions were encountered, making surgical removal of the mass extremely tedious and difficult. Six deaths were recorded, five of these occurring within a few days af-

ter operation. Causes of death were listed as status thymolymphaticus,[8] concurrent miliary tuberculosis,[5] postoperative shock and questionable hemorrhage into the peritoneal cavity,[7] and postoperative shock in two cases.[9, 23] The other death was possibly due to hemorrhage into the abdomen after a fall. Two of these tumors were apparently functional. Table I summarizes the salient features of the reported cases to date.

Embryology and Origin.—In the embryological development of the nervous system, certain cells, primitive neuroblasts, migrate from the neural crest to their future permanent sites and undergo further differentiation and development into ganglia of the sympathetic nervous system, chromaffin tissue, or Schwann cells. When this migration takes place, cells which are to form elements of the sympathetic nervous system do not differ in histological appearance from those which are to form the central nervous system; they differ only in their future developmental potential.[11] The differentiation of these primitive nerve cells, as well as the type of neoplasm which may arise from them in the various stages of differentiation, is graphically represented in Table II.

These migrating cells may not reach their future intended sites. They may begin to multiply at any time in their course of migration producing a neoplastic growth at that particular point. Some of these misplaced cells may become quiescent and remain as cell rests of embryonic origin in mature tissues. Proliferation of these cell rests may occur at any period of prenatal or postnatal development. Tumors containing mixtures of the several types of developmental cells and their end results may be found. However, these cases are rare. Wahl[28] reported one case in which neuroblastomatous, ganglioneuromatous, and chromaffinomatous elements were all present. Cases have been reported in which benign ganglioneuromatous areas have occurred in tumor masses, even though the major portion of the tumor mass was malignant.[29, 30, 31, 32, 33] Cushing and Wolbach[34] reported a striking case in which a malignant paravertebral sympathicoblastoma underwent full and complete maturation into a benign ganglioneuroma over a ten-year period.

The neuroblastoma is the type most commonly found in infancy and childhood. It may be formed of sympathogonia or sympathicoblasts or a mixture of the two. It most frequently occurs in the suprarenal glands. The only location in which primitive neuroblasts may occasionally be found in postnatal life is the adrenal cortex. Since these cells in this location differentiate later than other cells of the nervous system, Potter and Parrish[11] believe this may be a contributing factor to the very frequent appearance of neuroblastomas in the suprarenal glands.

Pheochromocytoma or chromaffinomas are very rare. They are usually found in the adrenal glands, the carotid body, the abdominal paraganglia and the organ of Zuckerkandl at the bifurcation of the abdominal aorta.

Neurofibromas have been reported repeatedly in the literature.

Ganglioneuromas are relatively rare in infancy and childhood.

TABLE I

NO.	AUTHOR AND YEAR	SEX	AGE	TUMOR SITE AND SIZE	SYMPTOMS	OPERATION	COMPLICATIONS
1.	Busse,[12] 1898	M	4 yr.	Lt. lumbar and pelvic	Swelling, lt. flank	Successful	None
2.	Ohse,[8] 1906	M	5 yr.	Lt. side lumbar spine	Abdominal swelling Always urinated small amounts	Successful	Death thought due to status thymo-lymphaticus
3.	Alezais and Imbert,[13] 1907	M	6 yr.	Precoccygeal size of a "nut"	Not recorded	Successful	None
4.	Braun,[14] 1908	F	6½ yr.	Below lt. kidney 17 × 14 × 14 cm. 1,900 grams	Swelling of abdomen from 1 yr. of age	Successful	None
5.	Peters,[15] 1913	M	3½ yr.	Rt. side lumbar spine 20 × 40 cm.	Swelling from birth	Successful	None
6.	Behan,[16] 1916	F	19 mo.	Lt. lumbar spine 5 × 4 × 1.75 cm.	Swelling, lt. flank	Successful	Dense adhesions
7.	Roman and Arnold,[5] 1924	F	3 yr.	Pelvic, retroperitoneal, spread through all organs	Asymptomatic, found during examination for acute febrile illness	Bladder portion of tumor biopsied	Inoperable, death due to concurrent miliary tuberculosis
8.	Neumann,[7] 1928	F	14 yr.	Pelvic, in both broad ligaments	Prolonged menstrual bleeding	Rt. side removed Lt. side inoperable	Death due to intra-abdominal hemorrhage
9.	Glaser, et al.,[17] 1950	F	4 yr.	Lumbar 7 × 6.5 × 2.5 cm.	Asymptomatic	Successful	None
10.	Toniolo,[18] 1950	F	4 yr.	Presacral, 4 masses 2—2.5 × 1.5 cm. 1—9 × 6 cm. 1—6 × 4 cm.	Asymptomatic	Successful	None
11.	Allende, et al.,[19] 1944	F	3 yr.	Lt. paravertebral	Asymptomatic	Successful	None
12.	Gatewood, et al.,[10] 1948	F	11 yr.	Rt. lumbar	Pain in L.L.Q. on urination only	Two stages ligated inf. vena cava	Bled to death through operative stab wound
13.	Murray and Stout,[4] 1948	F	9 yr.	Lt. lumbar 12 × 10 cm.	Asymptomatic	Biopsied only	Alive and well 25 mo. postoperatively
14.	Ribiero and Ferrari,[20] 1950	F	16 yr.	Lumbosacral 12 × 7 × 5 cm.	Asymptomatic	Successful	None

15.	Guillain and Bertrand,[9] 1952	M	3 yr.	3 parts (a) Lumbar and iliac (b) Into spinal cord (c) Behind psoas muscle	Pseudohermaphrodism Macrogenitosomia	Successful	Died of postoperative shock
16.	Bigler and Hoyne,[21] 1932	M	4½ yr.	Upper pole of rt. kidney 7 × 5.5 × 4 cm.	Celiac disease Idiocy	Chance finding at autopsy	
17.	This case, 1953	F	4½ yr.	Presacral 12 × 8.5 × 5.5 cm.	Asymptomatic	Successful	Sciatica, lt.
18.	Jackson and Babcock,[6] 1931	M	14 yr.	Lumbar and subdiaphragmatic 20 × 15 × 9 cm.	Increasing abdominal enlargement for 14 mo.	Incompletely removed	Densely adherent to aorta
19.	Solé and de Robertis,[22] 1935	M	16 yr.	Lumbar, trilobed, size of small cantaloupe	Abdominal swelling Anorexia, pallor	Successful	Densely adherent to aorta and ureter
20.	Blanco et al.,[23] 1934	M	6 yr.	Lt. lumbar extending to rt. lumbar area	Abdominal swelling for 3 years	Incompletely removed	Densely adherent to major vesssels Died of postoperative shock
21.	Wilmoth et al.,[24] 1933	F	16 yr.	Lumbosacral 28 cm. in largest diameter; 2 kg.	Abdominal swelling Operated 5 years before for abdominal "sarcoma"	Successful	Postoperative shock and urinary suppression
22.	Hortolomei et al.,[25] 1932	F	15 yr.	Rt. lumbar	Pain in rt. lumbar region	Successful	None
23.	Rapp,[26] 1913	M	4 yr.	Lumbar, paravertebral, size of a "nut"	Paraplegia	Successful	None
24.	Krayenbühl and Luthy,[27] 1947	M	4 yr.	T-12 to L-3, size of walnut	Paraplegia	Successful	Metastases, concurrent tuberculous spondylitis
25.	Yamada,[50] 1941	F	14 yr.	Rt. paravertebral, 1,400 grams	Paraplegia	Incompletely removed	Densely adherent to major vessels Died from postoperative shock
26.	Parreira and Prates,[51] 1934	F	16 yr.	Pelvis 6.4 × 4.5 × 3.5 cm.	Not recorded	Successful	None
27.	Parreira and Prates,[51] 1934	F	8 yr.	Lumbar 13 × 10 × 9 cm.	Increasing abdominal enlargement for 2 yr.	Successful drain—48 hr.	None
28.	Holubec,[52] 1938	F	† Schoolgirl	Lumbar	Not recorded	Successful	None

TABLE II

CELL TYPE	NEOPLASM	
I. Primitive neuroblasts (Sympathogonia)	I. Sympathogonioma	Neuroblastoma
II. Sympathicoblasts	II. Sympathicoblastoma	Neuroblastoma
III. → Ganglion cells	III. Ganglioneuroma	
III. → Schwann cells	III. Neurofibroma (Schwannoma)	
III. → Chromaffin cells	III. Pheochromocytoma (Chromaffinoma)	

Fig. 4.

Fig. 5.

Fig. 4.—Gross specimen.
Fig. 5.—Gross specimen, cut surface.

Gross and Histological Anatomy.—The ganglioneuroma is usually an encapsulated, firm mass with a more or less rubbery consistency, occurring singly or in multiples, sometimes lobulated and most frequently nodular in form. The cut surface usually presents a pale yellow or pinkish color and reveals a large amount of dense fibrous tissue which divides the tumor into numerous lobules. Both areas of degeneration and/or calcification may

be present. Microscopically the appearance is characteristic. "These tumors are made up of fully differentiated ganglion cells, often accompanied by their satellites, set in a dense stroma of sheathed neurites running in every direction."[35] Multiple sections from all regions of the tumor mass must be examined microscopically in the search for early undif-

Fig. 6.

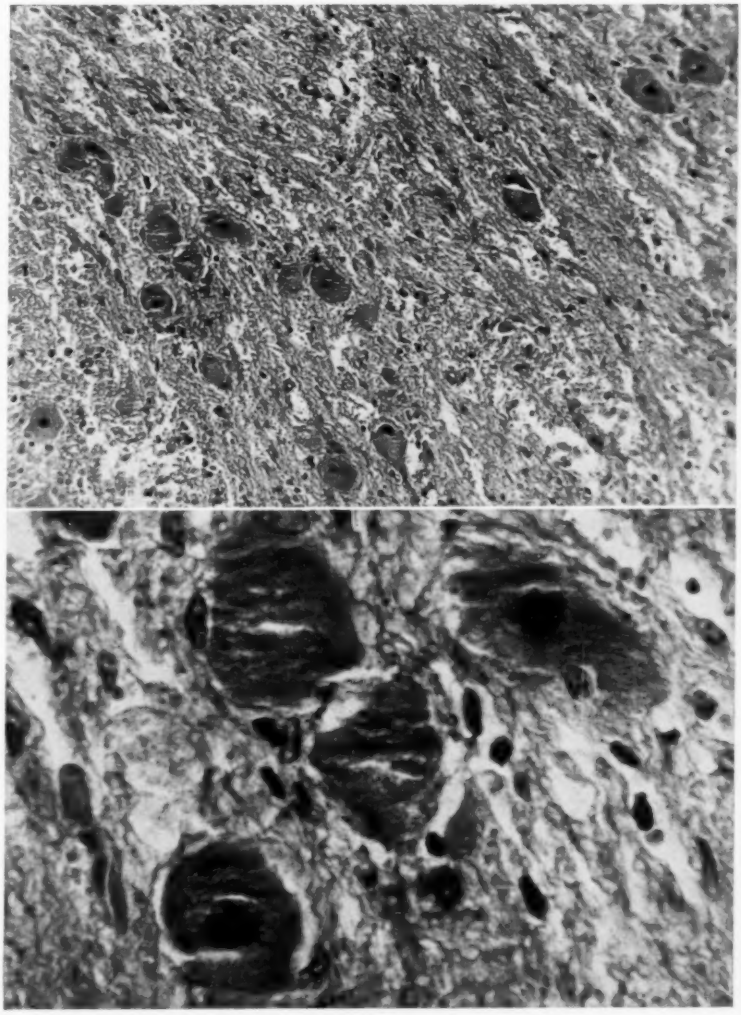

Fig. 7.

Fig. 6.—Photomicrograph, low power.
Fig. 7.—Photomicrograph, high dry power.

ferentiated cells. If none of these cells are present, the tumor is considered benign. Even though the microscopic examination revealed only mature ganglion cells, a benign ganglioneuroma in the case reported by Hawfield and Daisley[36] was apparently functional, producing an "Addison disease-like" complex which improved only with surgical removal of the tumor. Guillain and Bertrand[9] reported another case in which a benign ganglioneuroma was associated with pseudohermaphrodism and macrogenitosomia. In two cases[37, 38] an apparently benign ganglioneuroma produced metastases. The appearance of mature ganglion cells in lymph glands and other tissues immediately adjacent to a microscopically proved benign ganglioneuroma has raised the question of whether or not these tumors are actually malignant. According to Stout,[35] about 25 per cent of ganglioneuromas are not fully differentiated. Two forms apparently occur. One type contains a mixture of cells from undifferentiated sympathicoblasts to mature ganglion cells; 18 per cent of these metastasize. The other type contains in close approximation within the same tumor mass completely differentiated elements and characteristically malignant elements; 65 per cent of these metastasize.

Clinical Findings.—The clinical findings vary with the site, rate of growth, and size of the particular tumor mass. Ganglioneuromas themselves rarely produce any symptoms until they attain such size that they encroach upon neighboring structures. Small masses located in the pelvis, abdomen, or lumbar retroperitoneal area may grow for a number of years before symptoms are produced. Whereas, if growth occurs in the mediastinum or into the spinal canal, symptoms may result from relatively short growth periods. In Larson's[39] case symptoms were present from early childhood until operation at the age of 28 years. Pain in the right lower abdomen and back prevented the child from bearing her full weight on her right foot. However, no further symptoms were produced until the tumor growth became large enough to be palpable through the abdomen. In many instances discovery of the tumor came only at the time of active labor, when pelvic delivery became impossible because of obstruction of the normal outlet by the tumor mass.[40, 41, 42, 43] Ganglioneuromas are most frequently found within the thorax, in the posterior mediastinum, and chest wall. Extension of growth from the paravertebral area has been noted in a "collar-button" or "dumbbell" fashion between the intervertebral spaces and even within the spinal canal extradurally for moderate distances. It is important to note that ten cases in the lumbosacral area in infancy and childhood were subjectively asymptomatic. In eight cases abdominal swelling was the only objective symptom; in one, abdominal swelling had been present since birth. Necessity for a thorough examination of the abdomen in every infant and child at every visit or consultation cannot be overemphasized.

Roentgen examinations will disclose important information. Gastrointestinal series and intravenous pyelograms will serve to more accurately locate the tumor mass and show its ramifications. However, the appear-

ance of calcification in the mass may suggest the more common dermoid or teratomatous growth in preference to ganglioneuroma.

Ganglioneuroma must always be considered in an infant or child or young adult who is asymptomatic and presents on physical examination a firm abdominal mass.

Therapy.—Surgical removal of the tumor mass with pathologic study of the specimen is the only correct therapy. Roentgen therapy is valueless. Complete surgical removal affords the only relief from symptoms. However, this may be at times impossible or almost so. In most cases dense adhesions are encountered. In two cases[10, 44] it was necessary to doubly ligate the inferior vena cava to facilitate removal of the tumor. In other cases large arteries, veins, and ureters have been torn in the attempt to free adhesions.[45, 46] It is worthy of note that biopsy material from one of the cases considered inoperable[4] was successfully cultivated in vitro and the growth characteristics (division by mitosis) of the mature ganglion cells observed. Postoperative complications of particular interest have been peritonitis (one case),[41] ureteral fistula (one case),[45] increase in temperature in the lower extremity on the same side from which the tumor was removed (two cases),[39, 47] pain in the distribution of the sciatic nerve (this case), and transient peronal palsy (three cases).[3, 37, 45]

SUMMARY

1. A case of presacral retroperitoneal ganglioneuroma in a 4½-year-old child has been presented.

2. Review of the literature reveals that the incidence of ganglioneuroma in the lumbosacral retroperitoneal area in infancy and childhood is relatively infrequent.

3. Differential diagnosis of abdominal masses in infancy and childhood should include benign ganglioneuroma.

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FOOT PROBLEMS IN INFANTS AND CHILDREN

Rotational Deviations of Lower Extremities

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FEW problems are more disturbing to pediatrician and parent alike than that of the child who toes in or toes out. Most commonly, the problem is one of deciding whether or not to reassure an anxious parent that the condition is a self-limiting one—that it is a physiological variation of the normal. At present there seems to be no unanimity of thought as to what is normal and what requires treatment. Thus, the pediatrician asks himself three questions: (1) Can the parent be safely reassured that this is a self-limited condition which requires no treatment? (2) Are simple conservative measures which the pediatrician can recommend sufficient? (3) Is this a problem for the orthopedist? It is the purpose of this paper to outline a method for handling such problems.

THE PROBLEM

Four situations are most commonly met:

1. The infant or prewalker who holds his feet turned in.
2. The infant or prewalker who holds his feet (and legs) turned out.
3. The walking child who toes in.
4. The walking child who toes out.

1. *The Infant or Pre-Walker Who Holds His Feet Turned In.*—This may be caused by one of two things:

a. *Internal Tibial Torsion:* Here the entire leg below the knee is turned inward. Most infants are born with internal tibial torsion since it is the "fetal position" of the lower extremities. Spontaneous derotation takes place in the majority of cases before the infant starts to walk. In some, however, a persistent internal rotation of the entire leg below the knee in the older infant gives rise to concern by the parent. Frequently, one leg retains its internally rotated position while the other derotates to normal. For some unexplained reason, the left leg is the most comon offender.

In examining for internal tibial torsion, the infant is placed on his back. There are three key landmarks to observe: the anterior superior iliac spines, the patellae, and the second toes of each foot. Taking each lower extremity separately, first palpate the anterior superior iliac spine. Next, palpate the patella and turn the thigh so that the patella faces straight up toward the ceiling. Normally, a straight line drawn from the anterosuperior iliac spine through the patella should run through the second toe (Fig. 1). In internal tibial torsion, this line runs through the lateral border of the foot (Fig. 2).

Treatment. As mentioned before, most cases of internal tibial torsion spontaneously rotate to normal position before the child begins to walk. Therefore, it is perfectly safe to wait until the infant is at least 6 months of age before considering any active therapy. If the torsion is still quite marked beyond that age, a derotation bar may be used. This bar, which is a

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Denis-Browne splint attached to the shoes, may be adjusted to permit any degree of outward rotation (Fig. 3). It is worn day and night, removed only for bathing, for a period of four to six weeks. Then it may be used during naps and at night for an additional three to four weeks. The improvement is usually rapid and the brace is generally well tolerated by the infant.

b. *Metatarsus Varus:* This is the other common cause of toeing-in by the infant or prewalker. Occasionally, metatarsus varus and internal tibial

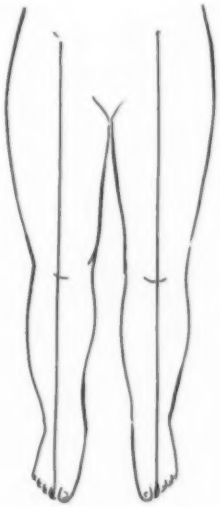


Fig. 1.—Normally, a straight line drawn from the anterior superior spine of the ilium through the center of the patella should be in line with the second toe. These are the key landmarks in aligning the lower extremity.

Fig. 2.—Internal tibial torsion of the left lower extremity. Right lower extremity is normally aligned. Patellae are outlined with skin pencil markings. Internal tibial torsion is the most common cause for toeing-in.

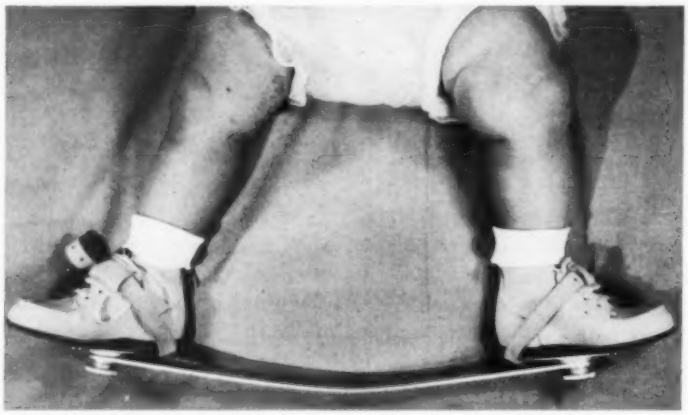


Fig. 3.—Derotation splint as used to hold legs in correct alignment for persistent or severe internal tibial torsion. Screw clamp on bar permits any desired degree of rotation.

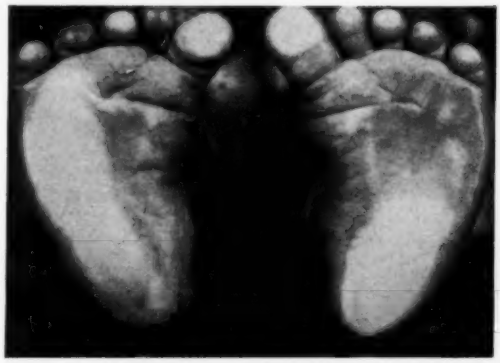
torsion may coexist. This condition, which has been termed "one-third of a clubfoot," is recognized by the fact that the toes turn inward in relation to the rest of the foot (Fig. 4, *A*).

The examination for metatarsus varus is easier when the soles of the feet are examined. Normally, the lateral border of the foot is a straight line. In metatarsus varus, the lateral border of the foot is convex (Fig. 4, *B*).

Degrees of severity of metatarsus varus vary from the mild forms in which the infant spontaneously corrects the turning in when the bottom of the foot is tickled, to the severe form where the foot cannot be manually straightened, even with the use of some pressure.

Treatment. In the mild form, where stimulation of the foot causes the infant to pull the toes into normal position, it is sufficient to wait and watch. The more contracted cases require active treatment by an orthopedist, usually manipulation and casts.

A.

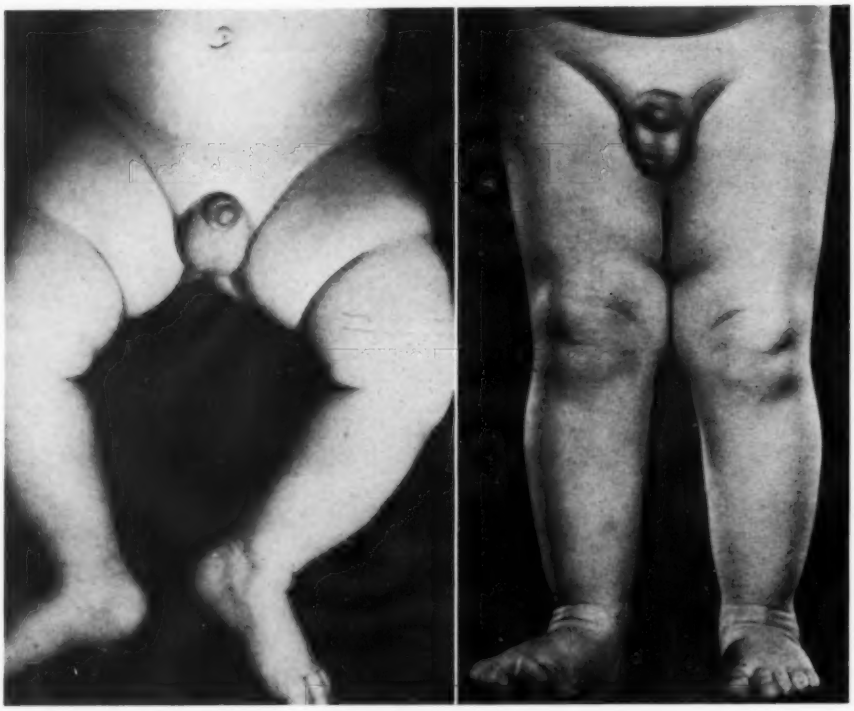


B.

Fig. 4.—*A*, Bilateral metatarsus varus. Forefoot is adducted in relation to the heel. *B*, Note the convexity of the outer border of the sole in metatarsus varus. Left foot shows severe degree of metatarsus varus. Right foot is involved to a much milder extent.

2. *The Infant or Prewalker Who Holds His Feet (and Legs) Turned Out.*—This is due to external rotation of the entire lower extremity from the

A.



B. *C.*

Fig. 5.—*A*, Derotation splint as used for correction of persistent or severe cases of external rotation attitudes. *B*, External rotation of the hips. Child lies with legs spread-eagled. They can be rotated inwardly only with difficulty. *C*, Same child as in Fig. 5, *A* and *B* following correction of external rotation of hips with derotation splint.

hips down. Usually, it is bilateral and occurs in infants with fat thighs (Fig. 5, *A*, *B*, *C*).

The examination is performed with the infant on his back. In this position, it may be seen that both lower extremities lie spread-eagled on the examining table so that the kneecaps point toward opposite walls of the room. If both thighs are grasped by the examiner and an attempt made to turn them in, it will usually be found that there is limitation of internal rotation. Whereas, normally, it should be possible to turn the patellae in so that they almost face each other; in infants with external rotation attitudes of the lower extremities, it is only with some force that the patellae can be made to point straight up.

Treatment. Since spontaneous correction here is the rule, it is permissible to apply very simple measures until the infant is 6 months of age. The mother should be instructed to apply only single-thickness diapers since any bulky mass of clothing between the thighs exaggerates the external rotation attitude. If the external rotation is still marked after 6 months of age, a derotation bar is employed in a manner similar to its use in internal tibial torsion. In external rotation contractures, of course, the feet are faced in by the bar.

3. *The Walking Child Who Toes In.*—One of two conditions causes a child to walk toeing-in. The most frequent cause, by far, is a persistent internal tibial torsion. A neglected or recurrent metatarsus varus or true clubfoot in a walking child accounts for the remaining few.

The child should, of course, be observed while walking to determine the degree of toeing-in and whether the involvement is unilateral or bilateral. The gait should be examined with shoes on and after removing them. Improvement in walking while barefooted may indicate that the shoes are too short. Finally, the feet and legs are examined for evidence of metatarsus varus and internal tibial torsion.

Treatment. The common observation that many children walk toeing-in while so few adults, without treatment, walk pigeon-toed, is ample evidence that spontaneous correction takes place in practically all cases. In many instances, it is sufficient to reassure parents that the condition is one which corrects itself. Certainly, in mild cases of persistent internal tibial torsion in children under the age of 4 years, nothing further is necessary. If the toeing-in is so severe that the child trips over his feet, the only effective treatment is one which derotates the tibias. This can be accomplished by a derotation bar between the shoes as previously described. Because of the difficulty of keeping an active child off his feet for four to six weeks, derotation bars at this age are used for two or three hours during the day and during sleeping hours. Twister braces may be used as an alternative. These permit walking but are cumbersome and expensive.

The treatment for neglected or recurrent metatarsus varus in the walking child is manipulation and casts.

4. *The Walking Child Who Toes Out.*—This condition is caused either by persistent external rotation at the hips or by pes valgoplanus (flatfeet) or both. The examination for external rotation at the hips has been described. Examination of the feet for pes valgoplanus should include observing the gait with and without shoes. It will

be seen that frequently the child wears the heels of his shoes down rapidly on the inner sides. In the standing position, attention should be directed to the ankles. In pes valgoplanus the ankles sag toward the inner side of the foot (Fig. 6). Observe, too, the longitudinal arch of the foot for its height.

Fig. 6.—Pes valgoplanus on the left, here associated with a mild genu valgum (knock-knee).

Treatment. When toeing-out is caused by external rotation at the hips, and is particularly awkward or unsightly, the use of a derotation bar may be justified. It should be worn at all times, except for a few hours during the day, and continued for from four to six weeks. After this, it may be continued as a night and nap splint for an additional six to eight weeks. In the child who is over 3 years of age, such appliances are not well tolerated. However, it is possible at this age to start gait training under the direction of a competent physical therapist.

Pes valgoplanus is a congenital deviation from the normal and is usually asymptomatic. If flatfeet are causing no pain and no difficulty with gait, all that is needed is for the child to wear good sturdy shoes which will not break down in the inner counter. (This is the stiff portion of the shoe that encases the heel.) Where the gait is awkward and the heel wears down on the inner side, an inner heel wedge of one-eighth to three-sixteenths of an inch is used. A Thomas heel may be used for the shoes of a child of 2 years and over. This is usually counterbalanced by an equal wedge placed on the outer side of the sole of the shoe. The two equal and opposite wedges do not cancel each other's effectiveness since the "normal" foot is one in which the forefoot is in slight pronation in relation to the heel.

Severe flatfeet which are painful and associated with an unsightly gait require more extensive orthopedic care. Arch supports made from tracings or casted models, rather than the so-called arch support shoes, are often indicated in such cases.

DISCUSSION

In the foregoing we have outlined what we feel is a rational approach to this common problem. There has been intentional omission of many commonly accepted measures because, in our hands, they have not been of therapeutic value. For the sake of completeness, some of these will now be discussed.

Manual Stretching.—This refers to the practice of instructing the mother in manipulation of the infant's feet. While there is no evidence to show that intermittent manual stretching, even when properly done, is effective, some justification for its use may be found. Certain parents are not secure unless some form of therapy is recommended. Gentle manipulation serves this need in a harmless and inexpensive way.

Reversing the Shoes.—This produces an effective optical illusion until the shoes have become molded by the feet. In mild cases of metatarsus varus it may help to hold the feet in the position of correction, after casts have accomplished actual correction.

Shoe Corrections for Children Who Toe In or Out.—The use of heel or sole wedges in order to correct the gait in the absence of flatfeet has been of no value in our experience. External rotation takes place at the hips and internal rotation at the knees or occasionally the hips. Shoe wedges do not influence gait variations due to these causes.

Foot Exercises.—In pes valgoplanus this modality has been recommended to "build up an arch." While exercises may help strengthen the intrinsic and extrinsic muscles of the foot, they will not manufacture an arch where one is congenitally absent. It is unnecessary trauma to parents to make them go through the anguish of trying to call an active child indoors from vigorous play to go through a series of monotonous foot exercises.

Shoes.—Shoes should be considered merely as a means of protecting the feet rather than as a therapeutic instrument. Until the child begins to stand there is no need to wear shoes except as protection against the cold. The first shoe is a high-top shoe with a soft or semirigid sole. After he has begun to walk, a more rigid sole is used. Ordinarily, high-top shoes are used up to about 2 years of age. The main reason for a high-top shoe is that the young child has a poorly demarcated heel until about 2 years of age. A low shoe or oxford will not stay on a foot until the heel is wide enough to fit into the counter. The main consideration to be given the selection of footwear is fit. A normal, healthy child with feet which are not deformed can wear anything which will protect his feet from cuts and the weather. A child with deformed feet will derive no benefit from a shoe besides the protection it affords. Indifference of the medical profession to this common-sense fact has permitted the exploitation of anxious parents by some unscrupulous shoe manufacturers.

WHAT TO TELL THE PARENTS

Most parents today can be approached with utter frankness. In many instances there is only need for reassurance and if the condition is simply explained they will be satisfied. We have had the opportunity to view this situation at close range, since one of the authors has a son who had both metatarsus varus and internal tibial torsion at birth. The metatarsus varus responded promptly to cast correction but the tibial torsion persisted until he was 3 years of age. In order to follow accurately its natural course, no treatment was undertaken for the internal tibial torsion. The condition spontaneously corrected itself by the time the child was 40 months of age. Even at 3½ years of age he toed in

when he was tired, but when told to "walk straight" he easily corrected this. (This is the earliest age at which most children will respond to direction.) During the child's first eighteen months as a walker there was considerable eyebrow raising among members of the family. The boy was very well-coordinated in spite of his awkwardness of gait, but it required considerable and repetitious reassurance to convince many well-meaning individuals that he was not "a shoemaker's child without shoes." The boy's mother, it should be noted, needed no convincing after trying to match his speed afoot.

This personal experience has led to a clearer understanding of the "heckling" by relatives and friends to which the parents are subjected. Parents in a situation such as this understandably have feelings of anxiety and fear that they are neglecting the child.

Based on this experience, it has been our practice, in situations where spontaneous correction can be expected, to carefully explain the condition to the parents. They are told that it is one which can be confidently expected to correct itself but that they must be willing to accept a certain amount of variation from what is considered normal gait for a year or two. They are told that in the more severe cases derotation bars can be applied and the chances of hastening correction are improved. The choice of awaiting spontaneous correction or of attempting active correction with derotation bars can sometimes be left to the parents. In this regard, however, if the physician senses indecision on the part of the parent he should make a firm recommendation for one or the other plan of treatment. Internal tibial torsion and external rotation attitude are the two main conditions which fall into this category.

There is less of a problem where active treatment is indicated. Parents readily accept cast correction for metatarsus varus or calcaneovalgus deformities, and shoe corrections for flatfeet.

SUMMARY

1. An outline has been presented for a rational approach to the problem of handling the child who toes in or toes out.

2. Causes for each of these situations have been enumerated.

3. The methods that we, as practicing physicians, one a pediatrician and the other an orthopedist, use to cope with these conditions are discussed.

SPONTANEOUS CHYLOTHORAX IN A NEWBORN INFANT

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THIS is the report of a case of apparently spontaneous chylothorax in a newborn infant with recovery.

CASE REPORT

Baby girl C was referred to the hospital at the age of 4 hours because of respiratory distress. She was said to have breathed spontaneously at birth; however, one hour later she was noted to be in moderate respiratory distress.

Prenatal history revealed that the mother was gravida v, para iv. The pregnancy was uneventful until thirty-six hours to delivery, when a blood-tinged vaginal discharge was noted. This persisted, labor pains began, and she entered the hospital about four weeks prior to the expected delivery time. The subsequent labor and delivery two hours later were uneventful. The stomach was not aspirated.

The infant appeared normal on admission except for moderate respiratory distress. The temperature was 97.8° F., the respiratory rate was 60, and the pulse rate was 140; the weight was 5 pounds 14 ounces. The thorax was symmetrical, but there was subcostal and intercostal retraction of the rib cage. The breath sounds were decreased throughout the right lung field and râles were heard on the right posteriorly. The rest of the examination was within normal limits. At this time it was thought that the infant had atelectasis, either congenital or caused by aspiration, or pulmonary hyaline membrane disease. On the second hospital day the respiratory rate averaged 40 per minute and the infant appeared improved clinically.

Initial urinalysis was normal. Initial complete blood count: red blood cells 4.28 million; white blood cells 19,900; hemoglobin 109 per cent or 16 grams. Several succeeding urinalyses and blood counts done during her hospital stay were normal.

X-ray examination of the chest showed almost complete opacification of the right hemithorax with only a small amount of inflated lung lying medially (Fig. 1). Mediastinal structures were shifted slightly to the left. On the third hospital day, repeat x-ray examination of the chest in the erect position showed better aeration, but the appearance was now that of extensive accumulation of pleural fluid on the right (Fig. 2). The mediastinal structures were shifted markedly to the left. The infant appeared to be in no respiratory distress then or during the remainder of her hospital stay.

On the fourth day the weight dropped to a low of 5 pounds 3 ounces. Feedings were started and were gradually increased to an evaporated milk formula. The first thoracentesis was done. Subsequent thoracenteses were done on the fifth and eighth hospital days. The color of the fluid from the first two thoracenteses was clear yellow, and the color from the third thoracentesis was a milky light yellow (Fig. 3). The characteristics of the pleural fluid are charted in Table I.

On the fifth hospital day the total serum protein was 5.09 Gm. per cent and total bilirubin was 9.3 mg. per cent, all indirect. Old tuberculin tests through $\frac{1}{100}$ were negative. A Bucky film of the chest taken immediately following the second thorarentesis revealed no underlying lung pathology. Further serial chest films showed reaccumulation of fluid until after the third thoracentesis. Thereafter, there appeared to be a slight decrease, but the fluid was still present by x-ray at the time of discharge.

From The Boston Floating Hospital.

Fig. 1.

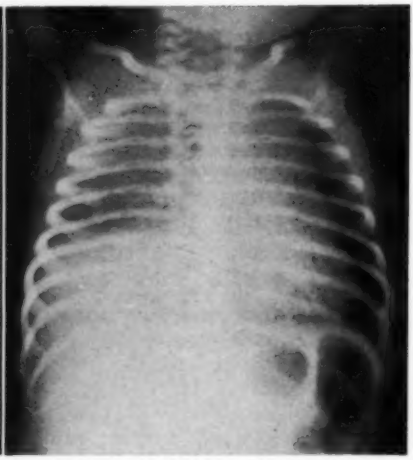

Fig. 2.

Fig. 1.—Recumbent film taken on second hospital day, showing complete opacification of right hemithorax with only a small amount of inflated lung lying medially.

Fig. 2.—Erect film taken on third hospital day, showing pleural fluid on the right.

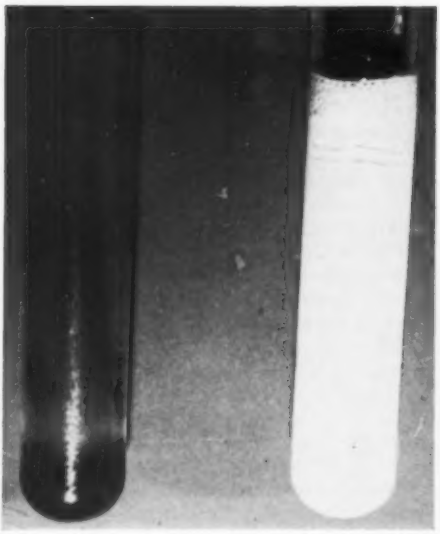

Fig. 3.

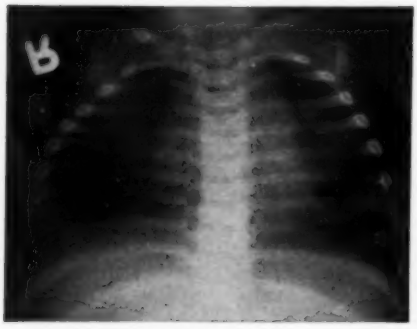

Fig. 4.

Fig. 3.—Tube on the left contains fluid from the second thoracentesis. Tube on the right contains fluid from the third thoracentesis.

Fig. 4.—Recumbent film taken at age 5½ months, showing an entirely normal chest x-ray.

On the tenth hospital day diarrhea occurred with no apparent cause. The infant was given fluids intravenously and then started on glucose and water by mouth. On three occasions when boiled skim milk was introduced, diarrhea began again. Finally, she was put on Nutramigen which she tolerated well; she was discharged on a Nutramigen formula on the twentieth hospital day.

When she returned ten days later, she seemed well and weighed 6 pounds 4 ounces. A repeat chest x-ray revealed a small amount of fluid.

The infant was examined again at the age of 5½ months. She had been well since discharge and was taking a whole-milk formula that she tolerated well. Weight was 15 pounds 1 ounce. Physical examination revealed nothing abnormal, and a chest film (Fig. 4) was interpreted as normal.

TABLE I

TAP	COLOR	SP. GR.	PROTEIN GM. %	CELLS	CULTURE	CYTOLOGY
1st	Clear orange yellow	1.012	3.10	28,700 99% lymphocytes	Neg.	Neg.
2nd	Clear orange yellow	1.016	3.29	21,400 95% lymphocytes	Neg.	
3rd	Milky light yellow*	1.015	4.07	7,300 98% lymphocytes	Neg.	Neg.

*Smear, culture, and guinea pig inoculation of this fluid was negative for acid-fast bacilli. Sudan IV stain was negative for fat globules, and shaking with ether did not clear the fluid.

BRIEF REVIEW

Chyle is an emulsion of fine fat globules in lymph. It is milky in color, has a specific gravity of 1.012 to 1.018, an albumin content of from 0.5 to 3.9 Gm. per cent, with a total protein of 3.0 to 8.0 Gm. per cent, and a fat content of 0.9 to 4.8 gm. per cent. Chyle must be distinguished from chyliform fluid which is a serous effusion in which chemical changes within the fluid, especially in the proteins, result in a lecithin-globulin combination, imparting a milky appearance to the fluid. Chyliform fluid is low in cholesterol and high in lecithins.

Everhart and Jacobs[1] reviewed the literature on chylothorax in 1939. They found sixty-nine cases of chylothorax, only five of which had occurred in infants 1 year of age or younger, and only one of these occurred in a newborn infant. They considered only four of the sixty-nine cases to be spontaneous chylothorax (i.e., without obvious cause). They added a case of spontaneous chylothorax that occurred in a 15-day-old infant. Since then, the report of only four other cases of spontaneous chylothorax and one case of spontaneous pleural effusion in the newborn infant has appeared in the available literature. Our case appears to be the seventh reported case.

Stewart and Linner[2] reported the first case in 1926. This 4-day-old infant was admitted because of respiratory distress and cyanosis. Birth occurred at home and was apparently normal. This infant required daily taps for relief of dyspnea and died 16 days after hospitalization.

Everhart and Jacobs[1] reported the case of a 15-day-old infant who was cyanotic with crying. At birth, the

umbilical cord was wound tightly around his neck and there was extreme cyanosis; vigorous attempts were made for revival. Thoracenteses were required for relief of respiratory distress every twenty-four to thirty-six hours, and death occurred on the twenty-first hospital day. Autopsy revealed a leakage of chylous fluid from a point in the posterior mediastinum, 1½ inches above the diaphragm; however, no duct was found.

Wessel[3] reported the case of a 2-week-old infant who had difficulty in breathing and circumoral cyanosis for twenty-four hours prior to admission. This infant required thirteen thoracenteses. With the onset of a diarrhea, no further thoracenteses were required. The diarrhea lasted for about two weeks and finally responded to a soybean formula. (Also, during this two-week period the infant had an otitis media that was treated with sulfadiazine and, finally, a myringotomy was performed.)

The case reported by Forbes[4] occured in a 2-week-old infant who was noted to have dyspnea and cyanosis soon after a normal birth at home. He was treated for pneumonia, but because of a poor response to therapy, he was hospitalized. Chest x-ray on admission revealed a bilateral pleural effusion. Subsequent thoracenteses revealed the fluid to be chyle. Over a two-month period forty-two bilateral thoracenteses were performed for relief of dyspnea, most of the fluid being obtained from the left side. In an attempt to maintain proteins and electrolytes, he was given chyle intravenously fourteen times without any difficulty. Absorption studies (feeding of a certain product to see how soon it would appear in the chyle) revealed that vitamins A and D were rapidly absorbed, but beta carotene was poorly absorbed. The infant finally died; at autopsy no thoracic duct or cisterna chyli were found.

Watson and Foster[5] reported a case in an 8-week-old infant with irregularity in breathing for one week prior to admission. Fourteen thoracenteses were required before spontaneous cessation of fluid accumulation occurred, and the cessation coincided with the onset of a mild diarrhea.

Sakula's[6] case occurred in a 5-day-old infant. At birth there was a slight delay in breathing (but nothing remarkable). At forty-eight hours, when the infant was put to breast, rapid respirations and slight cyanosis were noted; these became worse during the next two days. A thoracentesis was done on the fifth day of life and a second thoracentesis was required on the tenth day. The first revealed opalescent yellow-colored fluid containing no fat, and the second revealed odorless milky fluid with a yellowish tinge containing 0.9 Gm. per cent fat. After the second thoracentesis the infant did well with no further recurrence of fluid. The author stated that the delay between the onset of symptoms and injury, even though not apparent, was due to the fact that the thoracic duct was extrapleural. The interval represented the time required for erosion and perforation of the contiguous pleura by the enlarging retropleural collection of chyle.

DISCUSSION

Our own case presented several interesting points. There was no clear-cut evidence of trauma. The clinical course suggested the possibility of an injury to the thoracic duct during

labor or delivery; complete recovery seemed to rule out congenital absence or defect of the duct. The history of bloody vaginal discharge prior to delivery suggested the possibility of intrauterine anoxia that might have in some way caused rupture of the thoracic duct. Since intrauterine distress is relatively common and chylothorax in a newborn infant rare, other unknown factors must be involved in the etiology which remains obscure. Unlike the other infants reported, this infant was never critically ill, and thoracentesis was not necessary for relief of respiratory distress. Respiratory distress was noted for only the first forty-eight hours and cyanosis never occurred, although x-ray demonstrated that a large amount of fluid was always present.

Chylothorax was our first impression on x-ray findings, but the color of the fluid on the first two thoracenteses suggested the possibility of spontaneous pleural effusion. Only one case of spontaneous pleural effusion in the newborn could be found in the literature; this was reported by Cugell and Scherl[7] in 1949. This infant was noted to have marked respiratory distress fifteen hours after birth. Six thoracenteses over a twenty-seven-day period revealed dark orange fluid only. The effusion cleared up spontaneously after the last thoracentesis. The infant had been on an evaporated milk formula throughout the hospital stay.

After the third thoracentesis (the infant was then receiving a weak evaporated milk formula), the color of the fluid made the diagnosis obvious. Boiled skim milk feedings were started on the day of the second thoracentesis, and she had received her first milk feeding about one hour prior to the second thoracentesis. Since fat gives chyle the typical milky appearance (and since no fat was given in the formula until the fifth day of life), we did not expect to see typical chyle until after the onset of milk feedings.

When the contents of the third thoracentesis were examined microscopically, fat globules were not noted even with Sudan IV stain, and the addition of ether did not cause the fluid to clear. As a result of this, quantitative fat and cholesterol studies on the fluid, which might have demonstrated the presence of a minimal amount of fat, were not obtained. Why the fat globules did not stain is not known (perhaps the amount of fat present was enough to impart the typical color to the fluid, but was not sufficient to be seen by an inexperienced examiner). In the event of a fourth thoracentesis, in addition to obtaining quantitative lipid studies, a fat-soluble dye would have been fed just prior to the procedure. Dye would then have been present in the fluid if this were chylothorax. The infant's continued improvement rendered this unfeasible.

In the cases described by Wessel[3] and Watson and Foster,[5] diarrhea occurred coincidentally with the cessation of fluid accumulation. Diarrhea occurred also in our case; and while the time relationship was not clear-cut, we also did not note any further accumulation of fluid after the occurrence. There is no simple explanation for any relationship between cessation of fluid accumulation and diarrhea, but it is well known that fat intolerance is a common cause or factor in infantile diarrhea. If we were to postulate that these particular infants sustained a tear of their thoracic duct

and subsequent chylothorax, then associated with the repair of the tear, diarrhea occurred as the result of transitory impairment of fat absorption. It is interesting that of the seven patients mentioned in this paper, four lived, and three of these had this associated diarrhea.

SUMMARY

A case of apparently spontaneous chylothorax occurring in the newborn period is presented. Only six similar cases are recorded in the literature, death having occurred in three. This patient had a very benign course and recovered completely.

Treatment should be conservative since spontaneous recovery may occur; thoracentesis should be performed only for relief of respiratory distress once a diagnosis is made.

I wish to express my appreciation to Drs. James M. Baty and Marshall B. Kreidberg for their helpful criticisms in the preparation of this manuscript, and to Dr. Carroll Z. Berman for his help in selecting the roentgenograms.

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On Pyloric Stenosis

In a child about three weeks old, that died of watery-gripes some time since, and which I opened, I found most of the stomach, towards the upper orifice, and almost the whole fundus, in the same tender state with that of the child just now mentioned. But towards the pylorus, the structure was firm enough, as likewise that of the intestines, both small and great. The stomach was quite distended with curdled milk and victuals, with which the nurse had crammed the child, mixed likewise with some of the chalk julep, but the whole intestines were remarkably empty. There were no morbid appearances to be observed any where but in the stomach; and this *viscus* being so full, while the intestines were almost empty, it looked as if the disease had been chiefly owing to a spasm in the *pylorus*, which prevented the contents of the stomach from passing into the *duodenum*. Perhaps, cases of this kind are more frequent than is commonly imagined; and it might probably be owing to the tender state of the stomach, that the antimonial solution, which was given the child, had but very little effect; and I have commonly observed, that when vomiting or purging medicines, given to infants in a sufficient quantity, have not the usual effect, it is a very bad sign. What is remarkable, this was the third child (and they have never had any more) which the parents have lost at the same age, and in the same disease.

GEORGE ARMSTRONG (1777)

PNEUMONIA COMPLICATING ORAL THRUSH TREATED WITH MYCOSTATIN, A NEW ANTIFUNGAL ANTIBIOTIC

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THRUSH is a common oral infection in the newborn infant, caused by *Candida (Monilia) albicans*. Incidence of infection ranges from 18.3 to 20 per cent[1, 2] in some newborn nurseries. According to Anderson and associates "oral thrush developed in each instance in which *Candida (Monilia) albicans* was found in the mouth of a newborn infant but in no instance when only other forms of yeast were present." The same authors found that the average interval after birth for the development of clinical thrush was 8.2 days.

In the same report, a relationship between maternal vaginal moniliasis and oral thrush was pointed out and the possibility was suggested that infection may occur by contact other than directly from the vagina. Among the complications of oral thrush, pneumonia and esophagitis should be considered.

Adams[3] reported that of eight patients in whom thrush appeared at the same time in a nursery, five had to be treated because of respiratory distress. Dyspnea, cyanosis, leukocytosis, and fever were found to be present in the majority of these patients; a diagnosis of pneumonia was confirmed by x-ray. The same author suggests that the coexistence of "*M. albicans* and a staphylococcus played a concerted role." In one of these cases which was fatal, monilial pneumonitis was found on post-mortem examination.

Henderson[4] found a mortality of 1.5 per cent caused by monilial infections in newborn infants during a survey covering a period of three years.

Several methods of treatment have been recommended for oral thrush; topical applications of different antiseptics have been favored in a number of newborn nurseries. Recently, Mycostatin, a new antifungal agent derived from cultures of *Streptomyces noursei*, has been used experimentally with success.

This antibiotic exerts a strongly fungistatic action in vitro and in vivo against a variety of saprophytic and parasitic fungi and yeasts. It has eliminated or markedly reduced the number of Candida (Monilia) organisms in the stools of twenty-five adult patients in forty-eight to seventy-two hours, according to Sternberg and collaborators.[5] Mycostatin has low toxicity for experimental animals or human cells in tissue culture.[6]

Animal experimentation has shown that Mycostatin is poorly absorbed from the gastrointestinal tract after oral administration. In dogs, using that route, the drug was barely detectable in plasma after two and four hours. After oral administration to adult patients, however, small amounts of Mycostatin may be absorbed and can be detected in the blood.

From the Pediatric Service, Meadowbrook Hospital, Hempstead, New York, Eugene Stanchi, M.D., Chief of Pediatrics.

Mycostatin is a Squibb trademark.

Because of favorable laboratory and clinical evidence of low toxicity and high fungistatic activity, the drug was used for the first time on a premature infant whose prognosis was extremely poor.

CASE REPORT

Infant J. B., aged 3 weeks, was admitted to Meadowbrook Hospital, Farmingdale, Long Island, on Aug. 5, 1954, because of thrush and pneumonia. The infant was born in another hospital on July 14, weighing 4 pounds 11 ounces. Pregnancy and delivery were uneventful. On the tenth day of life he was discharged, and examined at home a few hours later.

A typical white tongue of oral moniliasis was found; otherwise the infant's general condition seemed good. One per cent aqueous gentian violet paint to the mouth was prescribed, with full directions being given to the practical nurse in attendance. By August 3 no improvement of the mouth was noted, and 2 per cent aqueous ferric chloride was ordered as a substitute for the gentian violet. Two days later the undersurface of the tongue, soft palate, gums, and posterior pharynx showed extensive involvement. On the tongue, several ulcerated and bleeding areas were present and edema was severe. Râles were heard over the right side of the chest. Cyanosis occurred from attempts at feeding by nipple.

On admission to the hospital the infant weighed 5 pounds 6 ounces. Temperature was 98.6° F. and remained within normal limits during the entire illness. The infant appeared malnourished and critically ill. Thick mucus was noted in the pharynx; mucopurulent nasal and oral discharges were observed and cyanosis was present.

Oxygen and repeated suction were administered, and 1 per cent aqueous solution of gentian violet paint resumed for two days. Cultures failed to reveal monilia in the presence of this dye. The following day the general condition deteriorated rapidly, with gasping respirations and mild asphyxia pallida. Feedings by dropper, spoon, cup, gavage, and special nipples were followed by severe choking and cyanosis and increased bleeding from the mouth. Parenteral fluids, glucose, normal saline, and M/6 sodium lactate were given, plus a transfusion of 32 c.c. of whole blood. X-rays of the chest confirmed the presence of pneumonia with massive emphysema and some atelectasis (Fig. 1). Râles were heard in both bases. Mild opisthotonos was observed. Choking was present which elicited cough. Penicillin 50,000 units was injected with streptomycin 100 mg. every eight hours, and Gantrisin 100 mg. orally every six hours were begun on the second hospital day. Consultants agreed on August 7 with the clinical diagnosis of thrush and complicating pneumonia. The same day, Mycostatin in a flavored powder was started, 1 teaspoonful (175,000 units) every six hours. The antibiotic was mixed in 1 ounce of milk and administered by spoon. Within forty-eight hours, edema and bleeding completely disappeared from the mouth; there was a reduction of viscid mucus, and only 20 per cent of the previously noted white areas was still visibly involved. Oral feedings were then feasible for the first time.

Twenty-five cubic centimeters of blood was given for support on account of the previous small oral intake, followed by parenteral fluids and plasma the next day.

The supply of Mycostatin flavored powder was exhausted on August 12 and 1 tablet (500,000 units) was given instead, four times a day. The tablets were crushed, mixed with 1 ounce of milk, and given by spoon. Coincident with this increase of dosage, looser, more frequent, and darker colored stools were noted. After six days (August 18) the flavored powder was again made available and 2 teaspoonfuls were given every four hours. Stools gradually returned to normal without special treatment.

During the subsequent week, further improvement gradually occurred in

the oral and pharyngeal mucosa so that the infant was able to take 2 to 3 ounces of formula by ordinary nipple. Respirations were less labored, but the infant could not be removed from oxygen except for short periods. In the course of the second week, x-rays showed slow but definite improvement of the pneumonia, confirming the clinical impressions.

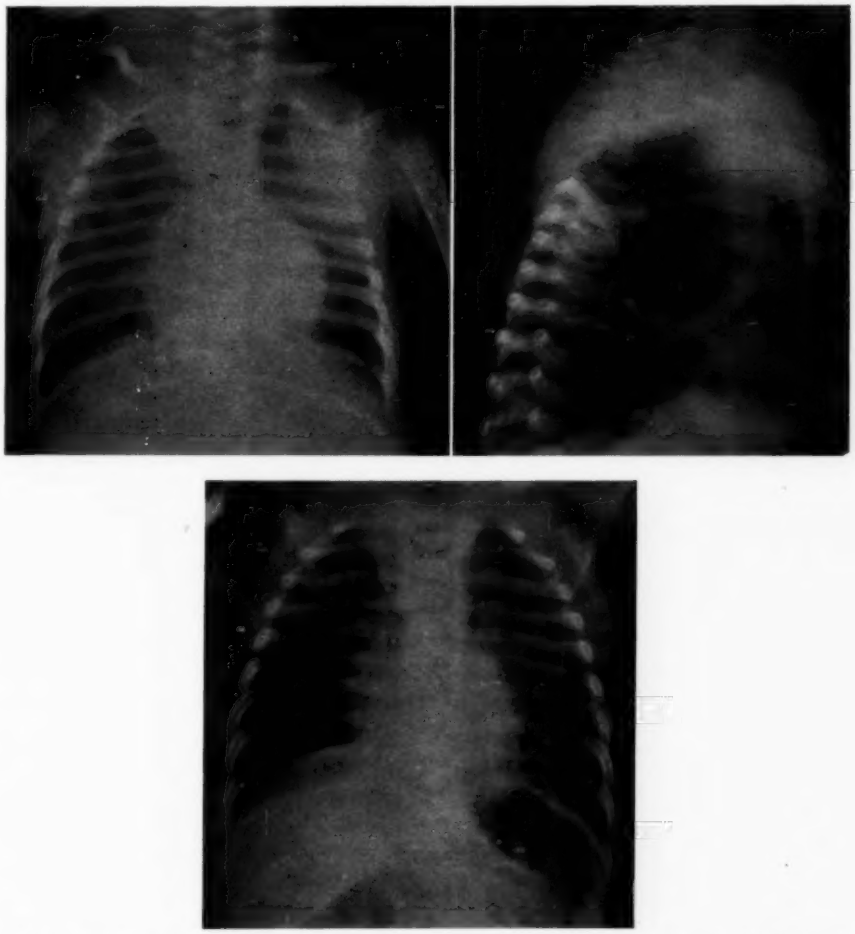

Fig. 1.—Representative x-rays taken on second, eighteenth, and twenty-eighth hospital days, showing multiple pneumonic, atelectatic, and emphysematous changes gradually progressing to normal.

The three special nurses on duty for twenty-four hours during the first week were reduced to one nurse covering one eight-hour period a day. The patient was able to tolerate one-hour periods out of oxygen and weighed 6 pounds by the end of the second week. One week later oxygen was discontinued.

Streptomycin was discontinued on the fifth hospital day and penicillin on August 23 (eighteenth day of hospitalization).

As a complication of repeated nasal and pharyngeal aspirations, a *Pseudomonas aeruginosa* infection appeared

in the nasal cavity during the fourth week of hospitalization which responded well to polymyxin B and gramicidin nose drops.

On September 4 (thirtieth hospital day) the infant was discharged home with a weight of 7 pounds 6 ounces. Gantrisin was given for one week more and the Mycostatin was stopped after forty-five days of continuous therapy.

On September 13, at the age of 2 months, a physical examination was nonrevealing, the infant appeared alert, and the weight was 8 pounds. At 4 months of age, an incarcerated hernia and a hydrocele of the cord were repaired without complications.

DISCUSSION AND COMMENT

The possibility of pneumonia as a complication of oral thrush has been considered by several authors.

The difficulty of establishing a definitive diagnosis of monilial pneumonitis in small infants during life is obvious. Symptoms such as dyspnea, cyanosis, leukocytosis, and fever are common with a wide variety of respiratory tract infections. Neither x-ray findings of the chest nor isolation of *Candida albicans* from the mouth provides conclusive proof. Sputum cannot be obtained from newborn infants, and the use of bronchoscopy for cultures has the disadvantages of unreliability and trauma. According to Kligman,[7] skin tests and serologic reactions have not as yet reached a decisive status as diagnostic procedures.

Even if post-mortem examination is carried out, a diagnosis of monilial pneumonia cannot be considered unequivocal. *Candida (Monilia) albicans* establishes itself frequently in pathologic tissue as a secondary invader.

Although in the case presented there may be some question of the definite diagnosis of monilial pneumonia, the evident oral pathology and subsequent lung involvement seem consistent with this impression. The problem of bronchopulmonary mycosis is discussed by Hamel[8] and others. A number of papers have appeared in the medical literature reporting moniliasis following the use of antibacterial antibiotics. The work carried out by Hazen and collaborators[9, 10] shows that the combination of *Candida (Monilia) albicans* and oxytetracycline or chlortetracycline given intraperitoneally to white mice killed them more rapidly than *Candida (Monilia) albicans* alone. The same authors confirmed the protective action of Mycostatin against the virulence-enhancing activity of oxytetracycline on *Candida (Monilia) albicans*.[9, 10]

The failure of antibacterial antibiotics and topical medication to check the spread of the thrush in the present case jeopardized the life prospective of the patient. As an added complication, supportive care by parenteral route had become increasingly difficult. The obvious improvement in the oropharynx in the first two days must be attributed to Mycostatin since no other drug being given could be related. This improvement of the local inflammatory lesions was followed by a favorable reaction of the respiratory involvement. The overcoming of the oral infection in this infant, whose small biological defenses were heavily taxed, seemed to be decisive in changing his clinical course. No adverse effects were noted that are believed due to prolonged use of this new product except for the slight diarrhea which disappeared spontaneously.

SUMMARY

A case of an infant affected with oral thrush and with pneumonia is presented. The monilial infection was found on the tenth day of life and did not respond to topical medications. A few days later there was a deterioration of the general condition with symptoms of severe respiratory distress. The antibacterial drugs given at the time did not relieve either condition.

The use of Mycostatin as an antifungal antibiotic brought about a rapid amelioration of the oral lesions. A clinical and roentgenological improvement of the lung condition was noted in the following two weeks. No adverse effects were noted from prolonged use of large doses, apart from a slight diarrhea. The infant was discharged home one month after admission.

Acknowledgment is made to the Squibb Institute for Medical Research, New Brunswick, New Jersey, for supplying the drug; to Dr. John Caffey, Professor of Radiology, Babies Hospital, Columbia University, for reviewing serial x-rays; and to Dr. Herbert L. Elias, Consultant in Pediatrics, Meadowbrook Hospital. Dr. Jerome Jay Zuslacht performed the surgery.

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To the Printers

The following melancholy Account may not be unworthy of Public Notice; therefore pray be so kind as to give it a Place in your next.

BROOKFIELD, MAY 17, 1763.

On the 9th Instant the little Son of Benjamin Adams of this Place, of about 5 Years old, as he was playing with a few Beans, which were prepared to plant, put one into his mouth and involuntarily swallowed it down his *Aspera Arteria* (or Wind-pipe.) All humane Aid was industriously afforded, but in vain; for in 48 Hours the Child expired in great Distress, and in all the Vigour and Floridity of Youth, amidst the Tears of affectionate Parents and a weeping Family. By the Consent of the Parents, and at the Desire of the Physicians present, the Thorax of the Child was dilated and the Bean was found considerably extended, about half an Inch above the Division of the Aspera-Arteria, into the two Branches which lead to each Lobe of the Lungs. It is remarkable, that while the Bean stuck in the Entrance the Child was in the utmost Distress, but after it had passed down to the Place where it was found, he had Ease, breathed freely, without much Coughing, till a few Hours of his Death.

MASS. GAZETTE AND BOSTON NEWS LETTER, MAY 26, 1763.

Medical Progress

RECENT DEVELOPMENTS IN THE USE OF TISSUE CULTURE

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WHILE the potentialities of tissue culture as a research method have been recognized for many years,[1] its use in diagnosis and related clinical fields was restricted by the somewhat complex procedures involved and by the problem of bacterial and mycotic contamination. Recent developments have solved many of these problems, and have shown that "within the limitations of the method, tissue culture permits a wide selection of cell types and tissues including those of man whose use as an experimental animal is limited."[2] Modern tissue culture, whether by depression-slide chamber method, flask suspension technique, or roller-tube implant procedure, may employ tissues from the human embryo, including brain, kidney, skin-muscle; more mature human tissue such as foreskin, adult tissues as those of uterus, kidney, etc., monkey testicular and kidney cells; chick embryo tissues; and the HeLa strain of cell established in tissue culture from cells obtained from epidermoid carcinoma of the cervix.[3] Aside from its use as a culture medium, this HeLa strain of Gey is of considerable interest. The establishment and serial propagation of human cancer in tissue culture is in itself an accomplishment, and these cells have been maintained in vitro since their derivation in February, 1951, from an epidermoid carcinoma of the cervix.

From the Department of Pediatrics, Baylor University College of Medicine.

VIRUSES IN TISSUE CULTURE

Since viruses carry out their complete "life cycles" only in the presence of living cells, tissue culture methods offered promising application in the study of viruses and their effects, having certain advantages over the use of the embryonated eggs and of experimental animals which are not always susceptible to strains responsible for human disease.

The idea of culturing viruses in tissue fragments was not new, and numerous investigators had been successful to some degree, or over short periods of time. As early as 1928 the Maitlands[4] and their co-workers had shown that the virus of vaccinia could be cultivated in a medium consisting of fragments of kidney tissue suspended in a mixture of serum and inorganic salts. However, for the study of virus from human patients the method had limitations, the most serious of which was bacterial and mycotic contamination. A new era was opened in tissue culture with the advent of antibiotics; appropriate antibiotic substances can be included routinely in the culture medium, and it is now possible to guard against the growth of fungi also by the addition of certain reagents apparently harmless to the cells, and not too

disturbing to the balance of the nutrient fluids. Contaminated material such as fecal specimens, nose and throat washings, vesicular fluid from skin lesions, biopsy specimens, etc., can be inoculated directly from the patient into tissue culture preparations.

Enders and his associates,[2, 5] and also investigators in other laboratories,[6] have made use principally of two tissue culture methods: the tissue-fragment suspension method of Maitland, in which minced tissue is added to a flask containing a buffered medium of inorganic salts and serum, the flasks being kept at constant optimum temperature; and the roller-tube method, in which tissue fragments are implanted by means of serum clot on the sides of glass tubes, in the bottom of which is the nutrient medium. These tubes are rotated slowly at an angle by means of a revolving drumlike holder in such a way that the tissue implants are bathed at frequent intervals by the nutrient fluid. The entire apparatus is inserted in an incubator, or constant temperature room. Virus is added to the nutrient fluid, and the cytopathogenic effect on the cells can be studied at intervals. In most instances, as virus multiplies in the cells, it is found free in the fluid in higher concentration; subcultures may be made by transferring fluid, or virus yield harvested by collection of fluid. The nutrient medium may contain an indicator, in order that changes in pH can be detected readily. These pH changes are important because they may indicate changes in the metabolism of the cells, or serve as an index of tissue breakdown due to virus activity. The effects of the virus can be neutralized by the addition of specific immune serum either from human patients during convalescence, or from experimental animals, immunized or convalescent. By such comparative means, strains of virus isolated from patients can be identified, and increasing titer of antibody during the course of clinical illness can be followed.[7]

Technical improvements in tissue culture methods are being made constantly: simplification of apparatus required,[8] the use of Cellophane supports for cell growth,[9] monolayer tissue culture,[10] culture of individual cells,[11] improvements in the nutrient fluids, including use of allantoic and amniotic fluids,[12] particularly bovine, various means of increasing virus yield, detailed studies of cytopathogenic effects, etc.[2, 5, 13] The present-day promising potentialities of tissue culture procedures are the result of innumerable contributions through the years by a large number of clinicians and research workers.

Poliomyelitis Virus.—Significant developments stemming from the isolation and study of strains of poliomyelitis virus in tissue culture received their first impetus a few years ago from the work of two groups of investigators. As early as 1936, Sabin and Olitsky[14] were able to culture one strain of poliomyelitis virus in preparations of human embryonic brain tissue, but were not successful apparently in serial propagation or in employing other tissues. Adapting tissue-fragment methods which had proved successful in the propagation of other viruses, Enders, Weller, Robbins and their associates were able to culture strains of poliomyelitis

virus in fragments of non-nervous human tissue, principally embryonic tissues such as skin and muscle, intestine, uterine tissue, and foreskin.[2, 5, 7] The use of other non-nervous tissue followed, e.g., testicular, kidney cells, etc.[3, 6, 7, 10, 15] All three types of poliomyelitis virus, Brunhilde (I), Lansing (II), and Leon (III) have been isolated and identified serologically by tissue culture methods. Histologic study of tissue fragments removed at intervals from inoculated tissue cultures, as compared with controls, confirms the cellular metabolic disturbances suggested by pH changes (indicator color changes), gives evidence of progressive cell damage, and may indicate the type of cytopathogenicity. This "degeneration of cells in vitro represents a criterion of viral infectivity quite as useful as the paralysis or death of experimentally inoculated animals."[16]

Isolation of virus from patients with clinical disease has been carried out extensively in a number of institutions.[3, 6, 7, 17] In the laboratory of Enders and his associates,[2] for example, 173 fecal specimens were examined during the period from 1949 through 1952, from which 116 strains of polio virus were isolated, a recovery incidence of 67 per cent. An infectious agent of some type was isolated in 75 per cent of the fecal specimens examined. Of the 116 specimens positive for polio virus, sixty-nine proved to be virus of Type I (Brunhilde), eleven of Type II (Lansing), and thirty-six of Type III (Leon). Analysis of the patients as to the nature of the clinical manifestations revealed that 95 per cent of the fecal specimens from patients with paralytic polomyelitis yielded virus. By means of tissue-culture neutralization tests, increasing titer of strain-specific antibody can be followed during the course of clinical recovery. Strains of polio virus grown in tissue culture may be employed as antigen for the performance of complement-fixing antibody tests.[7] Often virus can be isolated from the patient and its serologic type determined within ten days or less from the onset of illness.[2] Also, by these methods, epidemiologic aspects of, and immunity to, poliomyelitis can be studied and compared in various parts of the world, and antibody levels determined in a given population, whether in endemic or epidemic areas, as well as in patients convalescing from clinical disease.

While most of the earlier investigations of polio virus in tissue culture were carried out with uterine or human embryonic tissue, several groups of investigators turned almost simultaneously to the use of human or monkey testicular or kidney tissue.[5, 6, 7, 10] Ready availability of tissue in adequate supply is of great importance, particularly in extensive investigations. Such tissue culture studies carried out by many investigators in many laboratories have provided the background for the current development of effective vaccines for active immunization against virus diseases, principally poliomyelitis. HeLa strain cells are proving advantageous for the cultivation of virus, and Scherer, Syverton, and Gey[3] have shown recently that replicate cultures can be prepared with suspensions of HeLa strain cells which are useful for "the quantita-

tion of poliomyelitis virus, the measurement of poliomyelitis antibodies, and the production of virus."[3]

Current investigations of interest which may prove to be highly significant concern the experimental segregation and propagation in tissue culture of avirulent or noncytopathogenic variants of poliomyelitis virus.[18] Repeated passage in a given animal has long been recognized as a means of virus attenuation, and research efforts have been directed intensively toward devising ways and means of inoculating live viruses with minimal risk of producing a severe infection in the inoculated host. The greatest success achieved in this field has been by the use of natural mutants lacking the pathogenicity of the original stock virus, but possessing the same antigenic structure, as, for example, vaccinia-variola. A well-known mutant is the 17-D strain of yellow fever virus produced by, or occurring in, serial transfer of virulent virus in tissue culture; the agent immunizes effectively against yellow fever, but does not give rise to clinical manifestations of the disease. The avianized Flury strain of rabies virus is produced by adapting street virus to the chick embryo; the avianized virus is almost devoid of pathogenicity, yet immunizes effectively. Used extensively in the immunization of dogs, the modified virus has shown no tendency to regain its original virulence. In veterinary medicine, the same is true of distemper in dogs and in cultivated fur-bearing animals, of cattle plague, Newcastle disease of chickens, etc.

The segregation of avirulent, noncytopathogenic, but antigenically active variants of such virus strains as those producing poliomyelitis would be of great importance clinically. Changes in the host or in the culture medium, accompanying or leading to the emergence of a mutant strain, are not understood at present. However, so-called "incomplete" forms of virus have been recognized in investigative work for a number of years, especially among strains of influenza virus, and particularly in those studies where, for some reason, large inocula of virus were used. While apparently capable of "reproducing itself," the incomplete virus differs from the fully active virus particle in that it seems to be noninfective, less toxic, and in suspension the particle is sedimented at a slower rate than is fully active virus. It is possible that any one sample of culture medium inoculated with virus, or any one specimen, may contain some active and some inactive virus forms. Incomplete forms of virus have been detected in a number of plant diseases, and in some diseases of fowl. This field of investigation is at the present time an active and important one. The dynamics of virus multiplication, and of virus susceptibility and infection in the host constitutes an intriguing study for the virologist, and one requiring a fundamental approach.[20]

Coxsackie Strains of Virus.—Viruses of the Coxsackie group, the C viruses, have been isolated from patients with so-called summer grippe, epidemic pleurodynia, severe myalgia, etc. Certain nervous system signs have been recorded,[21] and myositis may be so severe as to simulate abortive or nonparalytic poliomyelitis. Herpangina, a well-recog-

nized summer illness of infants and young children, has been attributed to a strain of Coxsackie virus.[22] Four immunologically distinct strains, which were identified as Coxsackie, type A, have been isolated from the throat or from fecal specimens of infants showing typical manifestations of herpangina. Complications of Coxsackie infection are relatively infrequent, but may include pleurisy, pancreatitis, orchitis, and rarely aseptic meningitis with pleocytosis of the cerebrospinal fluid.[21] Strains of Coxsackie have been classified into Groups A and B, with a possible C group, several distinct strains identifiable within each group.[7, 23, 24] Some of the strains have been recovered incidentally from patients with paralytic and nonparalytic poliomyelitis, from whom polio virus also was isolated. These agents produce severe myositis and paralysis in suckling mice, with disruption of muscle fiber structure. They are cytopathogenic for human tissue in tissue culture, both non-nervous and brain tissue. Weller, Robbins, and their associates[25] observed marked differences in the cytopathogenic behavior of strains A and B, and of a third type of Coxsackie cultivated in tissue culture.

In suckling mice the induced disease has been studied in detail with recovery of virus from blood, heart, liver, spleen, and intestinal wall, as well as from intestinal contents.[26] Histopathologic changes indicate myositis in skeletal muscles with marked edematous separation of the elements and loss of cross striations. Regenerative activity begins early, and may be seen side by side with myonecrosis and inflammation.

Coxsackie viruses are widespread, having been isolated and identified in the United States, Canada, Europe, and Africa, with verifying epidemiologic antibody studies. The viruses have been recovered from sewage and from flies.[27] Study of the strains of Coxsackie virus is still in progress, particularly with reference to their tissue specificity, cytopathogenicity, and serologic relationships. In general, strains of Group A seem to be associated with herpangina and short-term pyrexias, and those of Group B with more severe manifestations, epidemic pleurodynia, severe myagia, and muscle weakness, and, infrequently, aseptic meningitis.[21] A recent report describes an outbreak of epidemic myalgia in which the dominant clinical manifestations were dull muscular pain and signs of meningeal involvement.[21] Eleven patients thus affected showed spinal fluid changes compatible with aseptic meningitis. Coxsackie virus, Group B, type 2, was recovered from stool specimens of four patients, isolated from the throat in one patient, and from the cerebrospinal fluid in another. Isolations were accomplished in HeLa cell tissue culture; cytopathogenic changes in these cells were marked, and the agents were identified subsequently as Coxsackie, Group B.

Varicella and Herpes Zoster.—The virus etiology of these two diseases, while generally accepted, has remained somewhat puzzling, since no experimental animal, with the possible exception of the monkey, has proved satisfactory. The etiological relationship between varicella and herpes zoster was suggested origi-

nally by clinical observations which seem to indicate that cases of herpes zoster can be contracted from patients with chicken pox. Observations in a number of experimental investigations have tended to support this clinical impression. Identical lesions, both grossly and microscopically, were produced in the skin of human volunteers when vesicular fluids from patients with these two diseases were injected into the skin. Elementary bodies similar in type have been demonstrated by means of the electron microscope in vesicular fluids obtained from skin lesions of patients with chicken pox and with herpes zoster. Goodpasture and Anderson,[28] and also Blank and his coworkers,[28] observed inclusion bodies in tissue fragments of human skin grafted upon the chorioallantois of the chick embryo, following inoculation with fluid from herpes zoster lesions. More recently by means of tissue culture, particularly skin-muscle preparations, cytopathogenic agents have been isolated from eruptive lesions in varicella and in herpes zoster which are of a similar nature as judged by their behavior in tissue culture.[29] These agents which have been propagated serially in human tissue, give rise to the same type of eosinophilic intranuclear inclusion body in tissue culture cells. It is of interest that multinucleate giant cells, of a type similar to those observed in the varicella lesion in man, appear in infected cultures. Both these agents are unusual in their tissue-culture behavior in that they do not appear in quantity in the culture fluids, as is the case with other viruses. For serial subculture, tissue fragments, as well as fluid, must be transferred at each subculture.[2]

Yellow Fever.—Strains of yellow fever virus were among the first to be cultivated successfully in tissue culture,[30] and satisfactory immunization against this disease over a period of years has constituted the classic example of a safe, effective vaccine against virus disease.[31] The virus was adapted originally from infected mouse-brain material, and propagated in minced chick-embryo cultures for numerous subculture generations. Early work with yellow fever virus helped to establish the principle that the presence of living cells is necessary for the multiplication of virus. Of paramount importance to the development of vaccines was the observation that this neurotropic and viscerotropic viral agent could be attenuated so far as infectivity was concerned without loss of its antigenic powers. Chick-embryo cultivated strains lost their infectivity for monkeys, but were shown to be effective in immunizing monkeys. Prolonged cultivation resulted in the so-called 17-D series for use as a vaccine against yellow fever in man. However, constant vigilance is exercised in preparation of the vaccine against return to virulent form.

Herpes Simplex.—Herpes simplex may be isolated from lesions of skin and mucous membranes, occasionally from spinal fluid or autopsy material in aseptic meningitis, and from stool specimens.[32] In human tissue culture, this agent has a diffuse cytopathogenic action with marked destruction of cells and the appearance of intranuclear inclusion bodies.[2] Recent studies have employed the L strain of

cells (Earle) derived from mouse subcutaneous tissue in an investigation of the cytopathogenic effects of the viruses of herpes simplex and of pseudorabies.[11] Pseudorabies, known in veterinary medicine as "mad itch," is primarily a disease of domestic animals. It may occur in man, however, and is characterized by cutaneous and nervous system manifestations. The virus multiplies in tissue culture, producing cellular destruction and intranuclear inclusion bodies similar to those considered characteristic of herpes simplex. Likewise, lesions seen on the chorioallantoic membrane of the developing hen's egg following inoculation with pseudorabies virus are similar grossly and microscopically to those seen following inoculation with herpes simplex.

True rabies, an entirely different type of infectious agent, can be cultivated satisfactorily in tissue culture only in the presence of living nerve cells. Cultivation in embryonated eggs, however, is highly successful, and the effective Cox-type vaccine is used widely at the present time.[19, 33] As in the case of yellow fever vaccine strains, the long-passage attenuated virus is carefully checked for any signs of reversion to a virulent form.

Infectious Hepatitis.—Attempts to cultivate the virus of infectious hepatitis are of particular importance, since etiological investigations in this disease have been dependent almost entirely upon human volunteers. Recent reports indicate that the agent multiplies in embryonated eggs and in suspended cell or implant cultures of animal tissues, specifically chick-embryo suspensions and roller-tube cultures of modified rabbit liver.[34] After numerous passages, clinical manifestations were produced in human volunteers by oral and subcutaneous administration of infected suspensions or of culture fluids. A skin-testing material (antigen)[34] is being prepared from infected embryonated eggs consisting of amniotic fluid exposed to ultraviolet radiation. Evaluation of these promising studies is in progress, dependent upon final identification of the agent isolated and cultivated, and upon the development of specific serologic methods.

Other viruses cultivated by tissue culture methods include foot-and-mouth disease, for which vaccine trials are in progress[35]; canine hepatitis which may possibly be related to distemper[36]; epidemic parotitis; Newcastle disease virus which, while primarily a disease agent of fowls, is responsible for a conjunctivitis and an influenza-like disease in man; epidemic keratoconjunctivitis, prevalent in industrial areas during World War II, the virus isolated from human eye washings, and presently in the process of identification and classification[37]; strains of influenza virus, the common cold virus currently being investigated; St. Louis encephalitis, Japanese-B encephalitis; Eastern, Western, and Venezuelan equine encephalomyelitis, certain other mosquito-borne viral agents causing encephalitis in man, West Nile, Bunyamwera, etc., and a number of viruses of particular interest in the field of veterinary medicine. Some of these agents are characteristically cytopathogenic in tissue culture; a few of them seem bound closely to the cells which they infect so that nutrient fluids do not contain high concentrations of virus.

In a number of these viral agents, cultivation has been possible in human tissue culture preparations: the West Nile, Bunyamwera encephalitis viruses in human lymph node[38]; Venezuelan encephalomyelitis virus in human uterine tissue[39]; the common cold in human embryonic lung tissue.[40] In the case of the common cold, cellular destruction is minimal and peripheral. Demonstration of virus multiplication was accomplished by repeated passage of small inocula in tissue culture, followed by transfer to human volunteers.[40] Influenza viruses, A and B strains, have been isolated and propagated directly from nasopharyngeal washings of patients in human embryonic lung and kidney tissue.[41]

Recent reports describe the isolation by tissue culture of cytopathogenic agents from stool specimens of patients, mainly children, suffering from an unusual epidemic exanthem.[42] Similarly, a cytopathogenic agent was recovered from human adenoid tissue undergoing spontaneous degeneration in tissue culture.[43] About this time, an agent, apparently very similar, was isolated from patients with an acute respiratory disease.[43] These two agents, cytopathogenic for HeLa cells, gave presumptive evidence of immunologic relationship.

Experimental study of the virus of measles has been essentially unsatisfactory in the past. Recently, however, cytopathogenic agents were isolated from blood and throat washings of children with typical clinical manifestations of measles.[44] Cultivation was accomplished in human and monkey renal epithelial cell cultures in which unusual and characteristic cellular changes occurred. Large vacuolated giant cells with many nuclei appeared in the infected tissue fragments which were apparently very similar to the syncytial giant cells observed in lymphoid tissue during the early stages of measles in human subjects. Intranuclear changes were also observed in infected cells, including margination of chromatin and the development of homogeneous acidophilic bodies. No virus was recovered from stool specimens in the case of these patients.

Inclusion disease of the parotid (cytomegalic inclusion disease) is very similar to salivary gland disease of animals. It is of considerable interest that the virus of mouse salivary gland disease has been grown successfully in tissue culture.[45]

Serial propagation of the intracellular parasitic protozoan responsible for toxoplasmosis has been accomplished in roller-tube cultures of mouse and human tissue, and in animal experimentation has been shown to undergo intracellular multiplication in adult mammalian macrophages cultivated in vitro. In roller-tube cultures of human tissues, "toxoplasma multiply freely, and in so doing produce a diffuse cytopathic effect."[20, 46]

Tissue culture cultivation of the rickettsiae has been employed for a number of years, both for investigative purposes and, in some instances, for the preparation of vaccines.[47]

SEROLOGIC STUDIES IN TISSUE CULTURE

In addition to the isolation of viral agents from patients by means of tissue culture and the determination of their serologic types within a relatively short time, increasing titer of antibody may be demonstrated during the course of clinical illness and recovery. Neutralization tests employing the patient's serum and known

specific immune serum may be performed in tissue culture; complement fixation may be carried out, employing antigen derived from tissue cultures infected with known virus. A micromethod for the detection of complement-fixing antigens has been developed, which is proving of very practical value in the identification of unknown agents isolated from patients and in the determination of their etiological significance.[20]

Recently, the fluorescent antibody technique of Coons and his associates[48] has been adapted for use in tissue culture studies, and is proving of value in the clarification of immunologic relationships among infectious agents.[49] This fluorescent antibody technique consists in the use of antibody conjugated with fluorescein as a specific histochemical stain for the localization of antigen in cells. The method is being employed for the detection of antigens of rickettsiae, virus, pneumococcus, Friedländer bacillus, leptospira, etc. A recent report describes the demonstration by this method of the antigenic properties of virus inclusion bodies.[49]

OTHER USES OF TISSUE CULTURE

Other uses of tissue culture include metabolic studies of cells, cell permeability, the action of various therapeutic drugs and chemical compounds on cells, the action of such substances as hydrocortisone on growth and behavior of cells in tissue culture, the effects of ACTH and cortisone on susceptibility to virus invasion, the stability and infectivity of virus at varying pH levels, the effects of antiviral substances, etc. Control of contamination and of nutrient-fluid balance in tissue culture has now reached the stage where bacterial studies are possible. In this connection a recent report[50] is of interest which concerns the use of human cerebellum and cerebral cortex cells growing in tissue culture for investigation of the effects of *Hemophilus pertussis*. Marked cellular changes follow inoculation of the tissue cultures with this organism. These changes can be arrested by the early addition of specific antiserum, with recovery of cell function. Other studies of strains of pertussis have shown the effects of this organism on ciliated epithelial cells in tissue culture.

Malignant tumor cells, as a rule, can be grown in tissue culture more readily than their normal counterparts, perhaps because the malignant cell has greater proliferative power in vitro as well as in vivo. Studies of malignant tumors have been enhanced by the use of tissue culture, including fundamental work on carcinogenesis, carcinogens, and attendant changes in cellular metabolism; practical applications in screening for antimalignancy compounds, and in clinical diagnosis.[51] In some instances, diagnostic verification and identification of the type of malignancy have been facilitated by cultivation of biopsy specimens in tissue culture. The inhibitory effect on tumor cells in tissue culture of certain antimetabolites,[52] which in similar concentration have no effect on normal cells, has been the object of considerable investigation.

SUMMARY

As has been pointed out by a number of authors, tissue culture methods, subject to continued improvement, offer in addition to their practical use in infectious disease many opportu-

nities for wider investigation of cell growth and metabolism under various conditions, of sensitivity reactions,[53] of the effects of antiviral, antirickettsial, and perhaps antibacterial substances, and of the processes involved in antibody formation.[16, 54]

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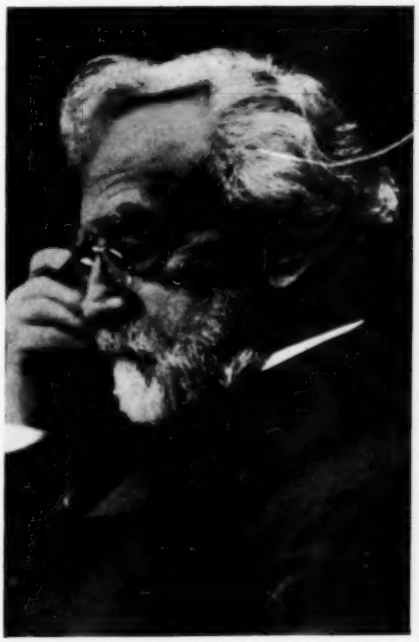
Pediatric Profiles

Abraham Jacobi

(1830-1919)



ABRAHAM JACOBI, the first professor of diseases of children in America, the pioneer of bedside teaching, the first president of the American Pediatric Society, the founder of the pediatric section of the American Medical Association, and the founder of the pediatric section of the New York Academy of Medicine, has done more than any other physician to place pediatrics in America on a firm and lasting basis. It is of interest to note that Jacobi considered himself a general practitioner, and that he did not believe in specialism. He was active in all branches of medicine. His thesis on admission to the New York Pathological Society bore the title "Concerning a New Treatment for Ovarian Cyst."

Born in Hartum, Westphalia, in Prussia, on May 6, 1830, of parents in moderate circumstances, it was said that his parents were advised not to expend much money on their child's education. They were told he was so sickly that he would live but a short time. In fact, Jacobi in later life attributed his small stature to inanition and lack of fresh air. Nevertheless, against his father's advice, Jacobi's mother persisted in giving him the best education that could be obtained for him. After high school he matriculated in several medical schools in Germany and Austria, as was the custom in those days, and graduated from the University of Bonn as a doctor of medicine in 1851. At that period there was financial depression and political discord throughout Central Europe. Freedom of speech and personal rights were everywhere restricted. There was practically no academic freedom. All speeches and publications were subject to censorship; and professors were watched to make certain they taught nothing of which the authorities and the government disapproved. After graduating from the University of Bonn, Jacobi made a trip to Berlin to take the state ex-

aminations, which would enable him to practice medicine. There he was arrested by state authorities, accused of being a revolutionist, and was imprisoned for nearly two years. He escaped from prison through the kindness of one of his jailors. His intimate friends, Carl Schurz and Ernst Kraekowitzer, had already migrated to America, and Jacobi made plans to follow their example. After a short stay in England, a country that did not appeal to him, he set sail for America and arrived in Boston following a long, rough trip. From there he went to New York where two hundred fifty thousand Germans already had preceded him, seeking a new home in a liberal country. Among these Germans were physicians, lawyers, artists, and writers. Some of them were young and some were old; some were unknown and some had left positions of distinction and honor behind them. Many of these had been forced to leave Germany on account of their participation in the revolution. A goodly proportion of them settled in New York.

In 1853 Jacobi opened an office for the practice of medicine on Howard Street in the Bowery. Two weeks later his first patient arrived. His charges at that time were twenty-five cents for office visits, fifty cents for home visits, and five dollars for confinement cases, provided the patient could afford that fee. Some sixty years later his office assistant told me that he had great difficulty in persuading Jacobi to increase his office rates from five to ten dollars. Throughout his entire medical career Jacobi included adults and infants and children in his practice. But he lectured and wrote and was interested chiefly in the care of infants and children. Shortly after his arrival in America, he translated foreign articles, mostly on diseases of infants and children, for the *New York Journal of Medicine*. He also lectured before a small group of students, his first topic being on diseases of the larynx in the young, and on laryngismus stridulus. Because of nervousness, he suffered an attack of laryngismus himself while giving his first lecture, but he mentions that he as well as all of his pupils survived.

Jacobi's first official position was that of Professor in Infantile Pathology and Therapeutics at the New York Medical College. Unfortunately that school had to close during the Civil War due to the fact that many southerners who attended the college had to return to their southern homes. It was in 1860, during his eighth year in America, that he published, in collaboration with Emil Noeggerath, a large volume on diseases of women and childen—at a personal expense of eight hundred dollars. The volume was not a very successful venture. The entire lot was finally sold for wastepaper at sixty-eight dollars.

In 1870 Jacobi was appointed Clinical Professor of Diseases of Children at the College of Physicians and Surgeons of Columbia University. This was the first professorship award in pediatrics in America, but it did not provide a seat on the faculty. It was some eighteen years later that the first full professorship of pediatrics, with a vote on the faculty, was awarded to Thomas Morgan Rotch at the Harvard Medical School. At the present time nearly every medical school in America has a department

of pediatrics with a full-time professor in charge, and a hospital for the instruction of infants and children.

In 1873 Jacobi was offered the professorship in diseases of children at the University of Berlin. Henoch, a famous pediatrician, was about to retire and it was thought that Jacobi might be willing to return to his native land as Henoch's successor. But Jacobi, after much deliberation, refused the offer. He appreciated the honor, but his love for America was great. And America loved and honored Jacobi.

During the sixty years of Jacobi's active medical life he wrote extensively on many medical subjects besides delivering innumerable addresses at medical societies, medical schools, medical and civil banquets, and at local, national, and international congresses. He published two volumes of his writings in 1893, dedicating and presenting them to his daughter, Marjorie, on her sixteenth birthday anniversary. In 1909 eight large volumes of his writings were published under the editorship of his friend, Dr. William Robinson. Jacobi contributed several chapters to Keating's *Cyclopedia of Diseases of Children,* and to Gerhardt's *Manual of Diseases of Children.* Jacobi's *Therapeutics of Infancy and Childhood* was published in 1895, with a second edition in 1897. His most important writings were on diphtheria, and intubation for diphtheria, before the days of antitoxin and immunization; on the many prevalent infections at that time; on the feeding and care of infants in and outside of institutions. His original methods of infant feeding are being employed at the present time with only slight modifications. He early advocated the use of boiled milk. He was among the fisrt to make use of intubation in laryngeal diphtheria after O'Dwyer's epoch-making demonstrations.

And Jacobi made the important observation, and lectured and wrote articles on this observation, that well infants have a much better chance of survival in even the poorest homes than in institutions. In his inaugural presidential address before the New York County Medical Society, Jacobi said, "I want to draw but one conclusion—that the attempt to raise babies in great institutions even with large means to aid you cannot be justified. These institutions must be given up and reserved for other purposes." And for these views he was severely criticized. He was finally expelled from the Nursery and Child's Hospital, where he was chief of staff, when he refused to resign. According to Dr. George L. Rohdenburg, who has written the history of Lenox Hill Hospital, Jacobi was one of the first in America to make use of the roentgen-ray machine. This was shortly after it was introduced in 1895. The medical service was then the most important service of the hospital, and had the machine under its direct supervision. Jacobi directed its use. Most of the examinations were by fluoroscopy rather than by photography. A despondent sailor shot himself in the head and survived the attempted suicide. He was admitted to Bellevue Hospital where the staff was hesitant to probe for the bullet lodged in the brain. The police account was definite that but one shot had been fired. The victim was transferred to our hospital for x-ray study. Jacobi was of the opinion that one of

the two bullets he saw was a reflection of the other, but which was to be considered the reflection he did not know. Today the answer would be that the police were in error, and that two bullets, not one, had been fired. The account is of interest as it shows Jacobi's enthusiasm for new discoveries.

Jacobi was one of the founders of the pediatric department of Mount Sinai Hospital. With the assistance of his German friends he founded the German Dispensary, and, later on, the German Hospital, now called the Lenox Hill Hospital. He was at one time or another attending physician or consultant at nearly every hospital of importance in New York City. With the help of Nathan Straus he established the first milk station to enable mothers with little means to obtain pure milk for their infants. He established the first preventorium for tuberculosis in infants.

In 1898 an assistant and very devoted friend of Jacobi's, Dr. Francis Huber, devised the plan of placing at the disposal of Columbia University a certain sum of money to pay for bedside instruction in pediatrics at Roosevelt Hospital. Sixteen beds were allotted and were named "The Jacobi Ward for Clinical Instruction." Third- and fourth-year students from Columbia were given instruction in pediatrics. This arrangement lasted only a few years. In 1910 Mrs. Anna Woerishoffer, a great admirer of Jacobi, gave the sum of one hundred thousand dollars, later on adding much more, to the German Hospital (now the Lenox Hill Hospital) to build a children's division of seventy beds in honor of Jacobi, and to be known as "The Abraham Jacobi Division for Children." This division was formally opened on April 18, 1915, with Jacobi in attendance. (Drs. Jacobi, Goodman, Van Ingen, and Leopold constituted the first staff members, only one of whom is alive at present.) A few years later the Francis Huber Fund was transferred to the Abraham Jacobi Division for Children of the Lenox Hill Hospital. From then until his death in 1919, Jacobi made frequent rounds with us at the hospital. I remember him well. He was a picturesque figure with a great capacity for human friendship. In cool weather he would appear wearing a large black hat with wide brim, and with a long black cape hanging loosely from his shoulders. We were not permitted to help him on with his cape when he departed—after sharing with us the coffee and cakes which were served after we had made rounds. He was of rather small stature, with large head, an abundance of gray hair, and a short beard. He had a kind sympathetic expression, and when he was with us he always had friendly words for every one of us. He was interested in all of our problems, and was forever imparting knowledge from his extensive experience. Everyone from the intern to the attending physician or visitor of highest rank profited when Jacobi made rounds. In those days there were very few complicated laboratory procedures; in fact, very little laboratory work was done. One or two interns usually took excellent care of our large service. Jacobi was always interested when new laboratory tests and scientific investigations were announced; he frequently spent much time with us and our

chemist, Adolph Bernhard, who demonstrated the various procedures.

I shall never forget one day on rounds when we showed Jacobi an infant who was in the process of recovering from severe intestinal intoxication. It was among the first cases which we had treated with the then new "Eiweiss" milk of Finkelstein and Meyer. The infant's stools had become normal in consistency, the dehydration had been taken care of, but in spite of everything the infant looked very sick, and was apparently a long way from complete recovery. Jacobi observed the infant for a few minutes and then inquired whether the patient was receiving orange juice. In our enthusiasm over this new method of treatment we had neglected to consider the ascorbic acid requirements of the infant. Jacobi knew at once what was wrong. Within a few days of the administration of orange juice the infant made a complete recovery.

Once every month, on Friday evenings, as I recall it, Jacobi invited his colleagues to present interesting cases at a small gathering of doctors at his home on East 47th Street. These meetings were attended by the most prominent physicians in New York. The cases and specimens were well prepared and demonstrated. Jacobi always joined in the discussion which followed. Cigars were passed around and, I believe, at the final meeting before the summer vacation a supper was served. Jacobi was most hospitable, and we of the younger group learned much from our association with the leaders of medicine in New York.

Few American physicians have been awarded as many honors as were bestowed upon Jacobi. He received honorary LLD.'s from Michigan, Columbia, Yale, Harvard, Jefferson, and Washington. He was elected the first president and president for the second time of the American Pediatric Society. He was President of the New York Obstetrical, the New York Pathological, the New York County and State Medical Societies. He was Honorary President of the International Medical Congress held in Paris. For many years he was President of the New York Academy of Medicine. He was honored with the Presidency of the Association of American Physicians and, finally, in 1911 he was elected President of the American Medical Association.

On the anniversary of Jacobi's seventieth birthday he was tendered a dinner attended by hundreds of his friends and colleagues. It had long been the custom in Europe when a professor had attained a certain high rank to be honored by his colleagues, friends, and pupils with a reception and a volume of original writings called a "Festschrift." The brilliant attainments and remarkable career of Jacobi's persuaded his friends that they were more than warranted in instituting such a testimonial in his honor on his seventieth birthday anniversary. It was an international "Festschrift," and it was the first of its kind to be given to anyone in America.

In 1873 Jacobi married Mary Putnam, daughter of the famous publisher, George Palmer Putnam. Mary Putnam was already a well-known physician in her own name. She was the sixth woman to receive a degree of medicine in America, and the first woman to be made a member of the

New York County Medical Society. Jacobi had been married twice before. Both wives had died shortly after marriage. There were two children from the last marriage, Ernst, who died at the age of eight years during a severe attack of diphtheria, and Marjorie, who is now Mrs. George McAneny, wife of the former New York Borough President. Mary Putnam Jacobi died in 1906, after suffering for many years from headaches and dizziness, which condition she herself diagnosed as a cerebellar tumor. This diagnosis was confirmed by Osler.

For more than fifty years Jacobi passed his summer vacations at Lake George. He had purchased property there and had built two cottages, one for his lifelong friend, Carl Schurz, and one for his own family. His honeymoon was spent there, and his only son, Ernst, was born there. Jacobi occupied his days walking through the beautiful woods and boating on Lake George. He had much time for reading and writing. His neighbors saw to it that he was never idle. When an expert was needed to treat or diagnose an unexplained fever, they did not hesitate to consult with Jacobi at his summer home. If a physician from a neighboring town had a difficult problem to deal with, Jacobi was the man to come to his aid. One summer on my way to deliver a paper before the Glens Falls Medical Society, I had dinner with Jacobi at his summer home. Always ready to render constructive advice, Jacobi said to me, "Make your remarks practical, so that the audience will not be bored."

In his eighty-eighth year, at night while he was sleeping, a fire destroyed Jacobi's home on Lake George. He was able to escape with his life by breaking a window and jumping a distance of ten feet to the ground. He suffered severe shock. His cottage was completely destroyed. Also destroyed were the first few chapters of his autobiography, which he had been writing for many weeks, and which he had been reading to his daughter the night before the fire. We urged him to rewrite his biography, but he was not so inclined. The autobiography would have been an interesting account of the birth and development of pediatrics in America.

The following summer Jacobi returned to Lake George and and occupied the Schurz cottage, but the surroundings were not the same there. His cottage was no more, and his treasures had been destroyed. Early that summer in his eighty-ninth year Jacobi passed away. Every honor which the medical profession could bestow had been given to him. Long before he died he had the satisfaction of seeing pediatric instruction carried on as a separate unit in almost every first-class medical school in America. There was a full-time professor of pediatrics at almost every medical school in the country. The children's hospitals everywhere were taking an active part in the prevention and in the treatment of diseases of infants and children. Scientific and clinical investigations in children in all its branches were being carried out. And Jacobi had been the pioneer investigator.

Shortly after his death the section of pediatrics of the American Medical Association founded "The Abraham Jacobi Memorial Fund." The

money from this fund was to be used to invite pediatricians of international reputation to present papers at the section meetings. It was decided that some of the moneys of this fund should be used to erect a lasting memorial to Jacobi at Lake George, the place he loved so much. The village of Bolton Landing agreed to make the site of the memorial a part of their park system. It is inscribed as follows: "1830-1919—In memory of Abraham Jacobi—Occupied the first chair of pediatries in America—A scholarly and broad-minded physician—Once President American Medical Association—Erected by his friends and colleagues—The Abraham Jacobi Memorial Fund—The American Pediatric Society—June 13, 1936." The memorial was attached to a large rock, and placed near the memorial bench which had already been dedicated in honor of Carl Schurz, Jacobi's friend for many years. Dr. L. K. Shaw called the dedication exercises to order. The memorial was dedicated by Dr. Isaac Abt, and by the Honorable George McAneny, Jacobi's son-in-law. Drs. L. E. LaFetra, F. W. Schultz and Herbert Willy Meyer, nephew of Jacobi, delivered addresses at the memorial exercises.

The memorial roadside park at Bolton Landing on Lake George. The stone at the right bears the bronze tablet dedicated to Dr. Jacobi.

Jerome S. Leopold

Comments on Current Literature

BATS AND RABIES

THE association between rabies infection and vampire bats, principally *Desmodus rotundus murinus,* has been well recognized in South and Central America for a number of years. As early as 1911, epizootics of a paralyzing fatal disease in livestock, known as *mal de caderas,* were described. Negri bodies observed in the brains of cattle dying of this paralytic disease identified the infection as rabies,[1] and transmission of the virus by the hematophagous vampire bat, an exclusive blood feeder, was surmised on the basis of observations by ranchmen. Subsequently (1916) rabies virus was isolated from the brain of a flat-nosed bat (vampire) captured in Brazil[2] while feeding on cattle during the day, and further investigation confirmed the transmission of rabies to cattle by the bite of blood-feeding bats. The occurrence of fifty-five human cases of rabies associated with an epizootic of paralyzing disease of cattle in Trinidad in 1925 suggested a relationship between the animal and the human infection. Virus was isolated from brain tissue and from the salivary glands of vampire bats in this area.[3] In connection with a similar outbreak of livestock disease in Mexico in 1944 (called derriengue), the virus of rabies was recovered from brain tissue of cattle, and from the brain, salivary glands, and saliva of vampire bats.[4] Comparable observations have been made in Honduras.[4]

Several reports appearing recently in American medical literature indicate that insectivorous bats in the United States are also infected with rabies virus, and that at least one proved case of rabies has occurred in a human subject thought to be the result of a bat bite. The isolation of rabies virus from the brain of a bat captured in Florida on June 24, 1953, following a daylight attack on a 7-year-old boy, established the fact that insectivorous, free-living, noncolonial bats do harbor the infection.[5] The boy received prompt medical attention, including rabies immunization, and made a complete recovery. Further isolation of virus was successful from six of 208 apparently normal insectivorous noncolonial bats captured within a radius of twenty-five to thirty miles of the initial positive specimen.

In September, 1953, a woman in Boiling Springs, Pennsylvania, experienced an unprovoked attack by a bat, and was bitten on the upper arm. Both touch preparations and sections of the bat's brain revealed typical Negri bodies, and inoculation of rabbits with brain tissue from this bat resulted in clinical manifestations of rabies within twenty-four to twenty-seven days following inoculation.[6] The woman who was bitten had prompt medical care, received antirabies prophylaxis, and did not develop rabies. Subsequently the bat in this instance was identified as the hoary bat, an insectivorous species that during the warm months of the year is widely distributed over the United States and Canada.

Another article of considerable interest appeared in the August, 1954, issue of *Public Health Reports,*[7] in which the recovery of rabies virus from naturally infected, insectivorous, colonial bats in the United States is reported for the first time. These bats from which rabies virus was isolated were collected in the central and south central parts of Texas. Three genera were represented in the collections comprising 200 bats: *Tadarida mexicana, Myotis velifer,* and *Pipistrellus subflavus,* in the order of their numerical occurrence. Insectivorous bats are present in large numbers in caves, ap-

propriate buildings, and shelters in the Southwest. Migration studies have revealed that bats from the Carlsbad Caverns in New Mexico fly as far as 800 miles into Mexico.[8]

While human subjects have been reported bitten by bats which subsequently were shown by appropriate studies to be infected with the virus of rabies, until recently no proved case of human rabies associated with the bite of a bat had been reported in the American literature. In the August, 1954, issue of the *Texas State Journal of Medicine,* Sulkin and Greve[9] report the case of a 43-year-old housewife who was transferred from west Texas to a Dallas hospital with symptoms and findings suggesting bulbar poliomyelitis. Inquiry into the patient's history revealed that in early October, three weeks prior to admission to the hospital and about sixteen days prior to the onset of her illness, the patient had investigated what seemed to be a dead bat. The animal proved to be alive, and the woman was bitten on the left forearm.

No particular ill effects were experienced from the bite for about sixteen days, when the patient began to complain of aching in the left arm and developed fever (103° F.). The fever continued, accompanied by nausea, vomiting, generalized aching, and inability to move the left arm. As difficulty in swallowing secretions increased, the patient was transferred to Dallas; tentative diagnosis—bulbar poliomyelitis. Lumbar puncture revealed 24 cells and spinal fluid protein, 74 mg. per cent. The patient's course was steadily downhill, and death occurred twenty-five days following the bat bite. Post-mortem examination revealed "encephalitis with demonstrable Negri bodies in central motor neurons compatible with rabies."[9] Unfortunately the bat was not available for identification and study; however, the sequence of events and the clinical course in this patient, together with the autopsy findings, strongly suggested the bat bite as the source of rabies infection.

A notation in the *Texas Health Bulletin,*[10] State Department of Health, for August, 1954, reports that at least five persons were bitten "by rabid non-vampire bats in the past year in Texas. All attacks were 'provoked,' that is, the bite victims had deliberately handled an obviously sick bat. All except one of the bites were sustained by children, the one exception being that of an eighteen-year-old Austin girl who handled a bat which had fallen into a pool where she was swimming. Two attacks have occurred in Austin, two in San Antonio, and one in Houston."[10]

The demonstration of rabies virus in colonial and noncolonial insectivorous bats in the United States has stimulated considerable interest in the habits of these winged quadrupeds, and has prompted studies concerning species ecology, feeding and migratory habits, et cetera. The enormous service rendered by insectivorous bats in insect control is reflected by the estimate that a "single bat (*T. mexicana*) will consume from one-half to its full weight in insects in a single twenty-four hour period."[11] Consequently wide-scale control of insectivorous bats does not seem justified at present, especially since information concerning the prevalence of rabies in these bats is limited. Knowledge as to the source of rabies infection in the insectivorous bats must await the results of migration studies now being carried out, especially in southern United States and in Mexico. "Certainly the destruction or abatement of the *Tadarida mexicana* is not justified, but it does appear that the public should be warned relative to the danger inherent in the handling of sick bats."[11]

RUSSELL J. BLATTNER.

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News and Notes

The following were certified by the **American Board of Pediatrics** at the examination at New Orleans, La., March 4, 5, and 6, 1955.

Dr. Esther Elizabeth Anderson, Louisiana State University School of Medicine, Department of Pediatrics, 1542 Tulane Ave., New Orleans 12, La.

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Dr. Richard Lucas Bagnetto, 5519 Elysian Fields, New Orleans, La.

Dr. Albert L. Ball, 1073 Madison, Memphis, Tenn.

Dr. Wilford Dean Belnap, Chief, Pediatric Service, U. S. Army Hospital, Ft. Belvoir, Va.

Dr. Truett C. Boles, U. S. Naval Hospital, Jacksonville, Fla.

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Dr. Hulda J. Wohltmann, 500 S. Kingshighway, St. Louis 10, Mo.

The next oral examination to be held by the Board will be in New York City, June 10, 11, and 12, 1955.

The Committee on **Prevention of Rheumatic Fever** of the American Heart Association issued a revised statement in January. Emphasis has been placed on eradicating streptococcal infections from the throat by the use of full doses of penicillin. For long-term prevention of recurrences of rheumatic fever, a daily oral dose of 200,000 to 250,000 units of penicillin taken before breakfast has been found adequate. The committee recommends that it should be continued throughout the year. The statement further includes recommendations as to the treatment of streptococcal infections, the protection of rheumatic fever patients in hospital wards, and prophylaxis against bacterial endocarditis. The recommendations will form the basis of a campaign to establish preventive rheumatic fever programs by the Association.

The **American Academy for Cerebral Palsy** will hold its annual meeting in Memphis, Tenn., Oct. 10, 11, and 12, 1955. The meetings are open to members of the medical and allied professions who are interested in cerebral palsy. Further details as to program and arrangements may be obtained from Dr. Robert A. Knight, Secretary-Treasurer, 869 Madison Ave., Memphis 3, Tenn.

The next annual meeting of the **American Institute of Dental Medicine** will take place at the Desert Inn, Palm Springs, Calif., Oct. 23 to 27, 1955. The faculty will consist of: Maury Massler, D.D.S., M.S., University of Illinois; Valy Menkin, M.D., Temple University Medical School; Hans Selye, M.D., University of Montreal; Reidar F. Sognnaes, D.M.D., Ph.D., Harvard School of Dental Medicine; Wendell L. Wylie, D.D.S., University of California. All Seminar lecturers will participate in a round-table forum, discussing the application of their subject to the practice of dental medicine. Applications and full information may be secured from the Executive Secretary, Miss Marion G. Lewis, 2240 Channing Way, Berkeley 4, Calif.

The annual **Cerebral Palsy Workshop** will be conducted in the University Hospital School for Severely Handicapped Children, State University of Iowa, Iowa City, Iowa, July 11-29, 1955. This workshop is designed for professional persons other than physicians, who are engaged in work with children having cerebral palsy. The course content is broad in scope. Registration is limited. Interested persons should write to Dr. R. R. Rembolt, Director, University Hospital School for Severely Handicapped Children, Iowa City, Iowa, for further information.

Beginning June 20, 1955, a course in the **Neuromuscular Diseases of Children with Special Emphasis on Cerebral Palsy** will be offered by Dr. Meyer A. Perlstein at the Cook County Graduate School of Medicine in Chicago. This is an intensive two-week didactic and clinical course in the diagnosis and management of the neuromuscular diseases of children with special emphasis on cerebral palsy, and includes field trips to itinerant clinics. Registration, which is limited, may be made by applying to the Registrar, Cook County Graduate School of Medicine, 707 S. Wood St., Chicago, Ill.

The **Children's Hospital of Philadelphia** will hold a **Centennial Medical Convocation** June 2, 3, and 4, 1955. In addition to members of the hospital staff, a number of foreign guests will present papers, including Professor Arvid Wallgren of Stockholm, Professor Fanconi of Zurich, Professor Gomez of Mexico City, Professor Alan Moncrieff of London, and Dr. Bernard Schlesinger, chairman of the medical staff of Great Ormond Street Hospital for Sick Children, London. Among the other guest speakers on the program are Drs. Edwards A. Park, Ernest Caulfield, Harold Faber, Mitchell Rubin, and Horace Hodes.

The **University of Pennsylvania Graduate School of Medicine** announces two short courses in **Pediatric Hematology** to be given at the Children's Hospital of Philadelphia in conjunction with the centennial celebration of the hospital: I. Practical Pediatric Hemology, June 6, 7, and 8, 1955; II. Rh and Other Blood Group Incompatibilities in Relation to Erythroblastosis Fetalis, June 9, 10, and 11, 1955. Address requests for application forms or other information to The Dean, Graduate School of Medicine, 230 Medical Laboratories, University of Pennsylvania, Philadelphia 4, Pa.

Prevention of Ophthalmia Neonatorum

At a meeting of the Board of Health of New York City on Jan. 13, 1955, the sanitary code was amended, permitting physicians to substitute an intramuscular injection of not less than 50,000 units of penicillin for the instillation in the eyes of newborn infants of a preventive for ophthalmia neonatorum.

In addition, whenever the Board of Health is of the opinion that the carrying out of the strict letter of this section is not necessary for the prevention of ophthalmia neonatorum, it may modify or waive the provisions of this section. In accordance with this provision, several hospitals have already asked for and received permission to further modify the preventive procedures.

Previous to this revision, the Code specifically stated that 1 per cent silver nitrate solution or a similarly effective agent had to be instilled in the eyes of newborn infants. This has been deleted in the revision. There is no mention of silver nitrate. The physician is directed to use "an effective agent" in the eyes of the newborn. Previously, also, a physician who wished to use penicillin parenterally had to request specific permission from the Board. In the present revision any physician may use not less than 50,000 units of penicillin in lieu of a local application of an effective agent for the prevention of ophthalmia neonatorum.

Book Reviews

Fisiologia y Patologia de la Alimentacion del Lactante. L. F. Meyer and E. Nassau, Cordoba, Argentina, 1954, Editorial Assandri.

A translation into Spanish of Meyer and Nassau's German text, *Physiologie und Pathologie der Säuglingsernährung*, by Alberto Chattás and Pedro León Luque of Argentina. The text will be useful to those who read Spanish but are unfamiliar with German.

Fibrocystic Disease of the Pancreas. Martin Bodian, M.D., New York, 1953, Grune & Stratton, 244 pages. Price $9.50.

A monograph by the pathologist of the Hospital for Sick Children, London, with the collaboration of Drs. A. P. Norman and C. O. Carter. The monograph is based on a series of 116 cases observed at the hospital over the years 1943 to 1950. Of these, 68 had died and 62 had been autopsied. After an unusually good historical discussion, the clinical material is presented. The series confirms, in a general way, the findings of other reported series as to genetic transmission, the variations in clinical severity encountered, and the importance of pulmonary infection on the course and duration of the disease. The most interesting part of the text is the presentation of the pathologic material by means of unusually fine, large illustrations. Bodian found involvement of the sublingual glands in every case, and considers Farber's conception of the disease as a congenital disorder of mucus production as correct. It is an interesting and unusually well-written monograph.

Lehrbuch der Tuberkulose des Kindes und des Jugenlichen. Prof. Dr. Med. Werner Catel, Stuttgart, 1954, Georg Thieme Verlag, 501 pages. Price $15.70.

The first edition of *Childhood Tuberculosis* by Prof. Catel of the University Children's Clinic at Kiel, published in 1950, has been extensively revised and enlarged. It presents probably the most thorough and extensive discussion of the subject available. Dr. Catel presents the subject in eight sections with several chapters under each. The sections include such subjects as the tubercle bacillus, allergy and activity, the primary infection, differential diagnosis, prophylaxis, and treatment. It is an exhaustive rather than a practical clinical discussion, and is a valuable addition to pediatric literature. It is well illustrated and excellently printed. Each chapter is followed by an extensive list of references and the book will be a useful reference volume for children's clinics and hospitals.

Malformaciones Congenitas de Labio y Paladar y su Tratamiento. Dr. Felipe Cacho, Mexico, D. F., 1954, Ediciones Medicas del Hospital Infantil, 154 pages.

Cleft Palate and Speech, ed. 3. Muriel E. Morley, B.Sc., Baltimore, 1954, Williams & Wilkins Co., 173 pages. Price $4.25.

These two monographs on cleft palate emphasize different phases of the problem. Dr. Morley's text, which first appeared in 1945, is chiefly concerned with the types of speech defect that occur and their treatment. It is based on an extensive experience as Speech Therapist to the Royal Victoria Hospital and The Hospital for Sick Children at Newcastle-upon-Tyne. Dr. Chaco, chief of the surgical service at the Hospital Infantil in Mexico City, is more concerned with the operation and corrective viewpoint, although he has an extensive chapter on speech training in the Spanish language. His material is based on 425 patients at the Hospital Infantil, and several of his colleagues have collaborated with him in the discussion of the anesthesiology and dental treatment. Both texts are excellently illustrated. There is no condition that calls for more teamwork than the treatment of cleft palate. It requires the close cooperation of the surgeon, the orthodontist, and the speech therapist if optimum results are to be obtained. Although each of these monographs is based on a special interest in one phase of the problem, both reflect this essential cooperation. Both authors have an extensive knowledge of the work and studies on cleft palate in other countries than their own.

Editor's Column

PLURAL BIRTHS

We have an Account from Petersburg in Russia, that a man had 72 children by two Wives.

By the first he had	*4*	*children at a Birth*	*4 times*	*16*
	3		*at a Birth 7 times*	*21*
	2		*at a Birth 10 times*	*20*
By the second Wife	*3*		*at a Birth 3 times*	*9*
	3		*at a Birth twice*	*6*
			Total	*72*

THIS remarkable report of fecundity was sent us recently by Dr. Ernest Caulfield, who had unearthed it from the *Boston Evening Post* of February 28, 1763. Fantastic as the report sounds, it is hardly more fantastic than the authenticated story of the mother of the famed Bushnell sextuplets, which we had run across only a few days previously in an interesting article by Dr. J. B. Nichols of Washington, D. C., "On Quintuplet and Sextuplet Births in the United States."[1] In 1865 Mrs. Bushnell, whose husband was a bookkeeper, gave birth to triplets, all of whom died within eight months. The following year the famed sextuplets were born, of whom four survived to old age. These were followed in turn by triplets and by quintuplets, none of whom lived. This authenticated record of seventeen births in four accouchements over a space of six years is almost as amazing as the unauthenticated report of the eighteenth century Russian family.

Nichols was able to collect seventeen cases of quintuplets, mostly well attested, and five of sextuplets. Of the sextuplets he considers two as well attested and three not completely verified. In addition, two instances of quintuplets, one the well-known Dionne quints, have occurred in Canada. Nichols discusses the report of seven or more births at one time, but finds none "can apparently be regarded as convincingly verified." The Bradlee octuplets, supposedly born in Ohio in 1872 and frequently referred to in medical literature, was a spurious case, as the report was later found to have been perpetrated in malice or as a hoax.

The rate for multiple births varies in different countries, and is higher in the Scandinavian countries, for example, than in the United States. Plural births are uncommon at the first parity, and for some reason or other are more numerous in the upper range of a woman's childbearing period. Thus in a total of thirty-nine instances of quintuplets, the age of the mother was 35 to 40 years in thirteen.

Those who are interested in the subject will find an excellent exhaustive discussion in a recent monograph by Miettinen, ***On Triplets and Quadruplets in Finland,***[2] based on 633 sets of triplets and 20 sets of quadruplets born in Finland between 1905 and 1952. In his series heredity played its usually accepted role, and the study confirms the older age of the mothers. The sex distribution of the infants was about equal, and among the quadruplets there was an equal number of boys and girls. In only three of

eighteen instances of quadruplets were the infants of the same sex. The intrauterine death rate for triplets was approximately five times that of the stillborn rate for all births, and the rate for quadruplets was somewhat higher. The infant death rate for the first year was higher than the rate for all infants, and only fourteen of sixty infants of quadruplet birth reached the age of one year.

The more common twins have been the subject of hundreds of reports since the study of Galton in 1876. Twins are interesting from the standpoint of psychologic similarities and differences as well as physical. For teaching growth and development nothing is more useful than the demonstration of several pairs of identical and nonidentical twins of different ages. The likenesses of the identical twins as contrasted with the differences in nonidentical twins as they grow and develop from birth to maturity strikingly emphasize the important role of genetics in the growth pattern. They demonstrate, moreover, the limitation of pediatric advice and care. To watch a pair of nonidentical twins of the same sex, reared in the same physical and family environment, grow from birth to maturity, and to note the marked differences in the physical, mental, and emotional makeup, and in health and resistance to infections is a real educational experience. It makes one somewhat skeptical of the importance of the implied value of child guidance and psychologic advice, which is so currently in fashion. Watching them grow up makes one wonder at times as to the extent that the pediatric and psychologic experts, who deal with environment, can really alter the genetic determinants which are so important in every child.

B. S. V.

REFERENCES

1. Nichols, J. B.: Acta Genet. Med. et Gemellol. 3: 143, 1954.
2. Miettinen, Maiga: Acta paediat. 43: 103, 1954.

ON EDITORIAL POLICY

FROM time to time the Editor receives letters protesting the publication of some article which has appeared in the JOURNAL. Usually the protest is due to a difference of opinion on the subject. The responsibility and policy of the Editor and Editorial Board have been commented upon several times in this column. Recently we ran across a statement written by a great editor and printer, Benjamin Franklin, in 1731. It so well expresses the editorial policy of THE JOURNAL OF PEDIATRICS, established a century later, that we feel it is worth reprinting. It expresses a fundamental philosophy that holds for medical journals as well as newspapers and magazines.

"It is likewise as unreasonable what some assert, *That Printers ought not to print any Thing but what they approve;* since if all of that Business should make such a Resolution, and abide by it, an End would thereby be put to Free Writing, and the World would afterwards have nothing to read but what happen'd to be the Opinions of Printers."